RESERVE

VOL. CL, No. 6 DECEMBER, 1915 No. 525

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JUN 8 1944

GEORGE MORRIS PIERSOL, M.D., EDITOR
JOHN H. MUSSER, JR., M.D., ASSISTANT EDITOR

OBITUARY OF EDWARD LIVINGSTON TRUDEAU, M.D. By RICHARD C. CABOT, M.D.

OBSERVATIONS UPON COMPLEMENT-FIXATION IN THE DIAGNOSIS OF PULMONARY TUBERCULOSIS. By CHARLES F. CRAIG, M.D. 781

LANDRY'S PARALYSIS: REPORT OF A CASE, WITH NECROPSY AND HISTOPATHOLOGICAL FINDINGS. By EDWARD D. FISHER, M.D. 791

THE VALUE OF SYMPTOMATIC DRUG TREATMENT. By JOSEPH L. MILLER, M.D. . 803

THE PROBLEMS OF NEPHRITIS FROM THE CLINICAL STAND-POINT. By ARTHUR R. ELLIOTT, M.D. 806

CHRONIC INTERSTITIAL NEPHRITIS AND ARTERIOSCLEROSIS. By OSKAR KLOTZ, M.D., C.M. 827

CERTAIN SYPHILITIC AFFECTIONS OF THE HEART AND AORTA. By J. M. ANDERS, M.D., LL.D. 835

A REPORT OF THREE HEART CASES SHOWING VAGUS INFLUENCE. By MONTGOMERY H. SICARD, M.D., and FRANK S. MEARA, M.D. 843

THE "SUGAR" CONTENT OF THE SPINAL FLUID IN MENINGITIS AND OTHER DISEASES. By ARTHUR H. HOPKINS, M.D. 847

TUBERCLE BACILLI NOT STAINABLE BY ZIEHL: THEIR CLINICAL SIGNIFICANCE. By CHARLES N. MEADER, M.D. 858

HODGKIN'S DISEASE: A STUDY OF A SERIES OF TWENTY-FIVE CASES. By W. F. CUNNINGHAM, M.D. 868

THE CITRATE METHOD OF BLOOD TRANSFUSION IN CHILDREN. By RICHARD LEWISOHN, M.D. 886

OWNERS AND PUBLISHERS
Philadelphia LEA & FEBIGER New York

COPYRIGHT 1915, BY LEA & FEBIGER. ALL RIGHTS RESERVED. ENTERED AT THE POST-OFFICE AT PHILADELPHIA AS SECOND-CLASS MATTER

PUBLISHED MONTHLY. SUBSCRIPTION, FIVE DOLLARS A YEAR, POSTPAID

This is the seventh of a series of articles on the uses of Stanolax—tasteless, odorless, liquid paraffin

The facts presented in this series of announcements are based on authoritative clinical data

Made from American Petroleum

To Correct Intestinal Stasis

When there is a retention of feces along the intestinal tract from which the patient may show symptoms of auto-intoxication, and yet have regular daily movements or even diarrhoea, STANOLAX—liquid paraffin—is of unusual value as a treatment.

STANOLAX lubricates the entire tract and dissolves all the hardened fecal matter that may be retained above the colon or lodged in the "kinks" of the intestines.

At the same time, STANOLAX is a protective agent—absolutely non-irritating; in fact liquid paraffin has been described as an "artificial intestinal mucous."

Stanolax Liquid Paraffin

Lane, Sir W. Arbuthnot (Guy's Hosp. Ga., Lond., 1911, XXV, 403; Lancet, 1911, II, p. 1540; Brit. Med. Jour., 1913, II, p. 1126; Proc. Roy. Soc. Med., 1913, VI, p. 49; Surg., Gynec. and Obst., 1913, p. 600): Most of the toxic intestinal substances are absorbed in the small bowel, though he attributes the primary cause of the trouble to the colon. It is here that the first stasis occurs, causing the colon to sag and to pull upon its mesenteric attachments, producing thereby sharp kinks and turns in the small intestines instead of the gradual and rounding loops of the normal gut. These kinks represent points of tractions and in time are accentuated by a thickening of the mesentery at these points. Lane advises that such cases should not be treated with laxatives, large quantities of water, buttermilk, etc., because little progress is possible under such treatment. For this condition — intestinal stasis —he recommends liquid paraffin as an ideal remedy.

* * * * *

A trial quantity and fully descriptive booklet will be sent gladly on request.

STANDARD OIL COMPANY
(INDIANA)
CHICAGO, U. S. A.

(429)

PROGRESSIVE MEDICINE

QUARTERLY ILLUSTRATED — **Paper, $6.00; Cloth, $9.00, per annum.** — 1200 PAGES POSTPAID

EDITED BY

HOBART AMORY HARE, M.D.

Professor of Therapeutics, Materia Medica and Diagnosis, Jefferson Medical College, Philadelphia

ASSISTED BY

LEIGHTON F. APPLEMAN, M.D.

Instructor in Materia Medica and Therapeutics, Jefferson Medical College, Philadelphia

A QUARTERLY DIGEST, PUBLISHED IN MARCH, JUNE, SEPTEMBER AND DECEMBER, COVERING THE ADVANCES, DISCOVERIES AND IMPROVEMENTS IN EVERY DEPARTMENT OF PRACTICAL MEDICINE AND SURGERY

At a very nominal cost per year the reader of PROGRESSIVE MEDICINE secures in four compact octavo volumes, in form which makes it available at a glance, all that the world's vast periodical literature devoted to medical topics affords of real progress and of permanent value. To cull from the important medical magazines, printed in the language of every civilized country, the announcements which embody the real progress of medical science; to assemble, weigh, and digest them; and finally to present them in usable form, is a task for the master-minds of medicine. Its successful accomplishment in PROGRESSIVE MEDICINE calls for the annual expenditure for periodicals alone of more than $1,200 and of time and special training the value of which is beyond estimate.

PROGRESSIVE MEDICINE thus performs an indispensable service by making available without delay, in small compass and at slight cost, the facts of the world's medical progress, and by pointing out their significance. This service could be obtained otherwise only at an expense and cost of time beyond the means of the busy practitioner.

SPECIAL COMBINATION OFFER

PROGRESSIVE MEDICINE (Paper) $6.00
THE AMERICAN JOURNAL . . . . . 5.00 } **BOTH, $10.00**

THE PRACTITIONER'S VISITING LIST

For 1916. Just Ready. — **Price, Postpaid, $1.25, net.**

With One Year's Subscription to Progressive Medicine or The American Journal, 75 Cents.

PRESERVES THE RECORDS OF DAILY PRACTICE. RELIEVES THE MEMORY. SAFEGUARDS THE DATA DESIRED FOR PERMANENT RECORD.

No physician in active practice can afford to be without this indispensable convenience. The ruled blanks offer a simple, complete and wonderfully adaptable system for recording the details of daily practice. Additional blanks provide for addresses, general memoranda, cash account, etc., while specially arranged pages provide a means for recording important data desired for permanent preservation.

POCKET SIZE

Wallet-shaped, clearly printed on fine tough paper suitable for pen or pencil and very strongly bound in handsome grained flexible leather, with flap, pocket, pencil, and two-year calendar, it is an essential part of the physician's equipment. Offered in four styles to meet the varying needs of different practitioners.

WEEKLY	MONTHLY	PERPETUAL	60-PATIENT
Dated For 30 Patients.	Undated. For 60 Patients Per Month.	Undated. For 30 Patients Weekly per Year.	Undated. For 60 Patients Weekly per Year.

The weekly, monthly and 30-patient perpetual contain 160 pages of classified blanks and 32 pages of data. The 60-patient perpetual consists of 256 pages of blanks alone.

READY REFERENCE DATA

In addition to the useful record blanks the Visiting List contains 32 pages of condensed data, ready for immediate use, including tables of weights and measures and comparative scales, tables of eruptive fevers, a scheme of dentition, instructions for uranalysis, poisons and antidotes, incompatibles, directions for effecting artificial respiration, an extensive table of doses, an alphabetical table of diseases and their remedies, and directions for the ligation of arteries.

706-8-10 Sansom St. PHILADELPHIA

LEA & FEBIGER

PUBLISHERS

2 W. 45th Street NEW YORK

NEW WORK **JUST READY**

DISEASES OF THE

BRONCHI, LUNGS AND PLEURA

By FREDERICK T. LORD, M.D.

Visiting Physician, Massachusetts General Hospital and Channing Home for Consumptives; Instructor in Clinical Medicine, Harvard Medical School.

Octavo, 605 pages, with 93 engravings and 3 colored plates.
Cloth, $5.00, net.

The author's comprehensive grasp of essentials and his emphasis on the very points on which the practitioner seeks light give this work a peculiar value. This is enhanced by his treatment of various respiratory disorders in their relation to tuberculosis and his extremely full exposition of points essential to differential diagnosis in conditions simulating tuberculosis. This last-named feature makes the book a practical necessity to every practitioner called on to diagnose tuberculosis and to every specialist in its treatment. The importance of the early diagnosis of aspirated foreign bodies is emphasized and the symptoms stated in detail. Attention is afforded the surgical aspects of empyema, of actinomycosis and echinococcus disease of the lungs. The importance of *x*-ray examinations and the significance of radiographic findings are made plain. The etiology and pathology of each disease receive due consideration. Symptoms are given in detail, as are the microscopy and bacteriology. Prophylactic measures, whenever possible, are presented, and directions for treatment are minutely complete.

DISEASES OF THE

RECTUM AND COLON

By JEROME M. LYNCH, M.D.

Professor of Rectal and Intestinal Surgery, New York Polyclinic; Attending Surgeon, Cornell Dispensary; Fellow of the American Proctologic Society, New York Castro-Enterological Society, etc.

Octavo, 596 pages, with 228 engravings and 9 colored plates.
Cloth, $5.00 net.

This is a literary and pictorial presentation of the best modern technique, affording a safe guide in the treatment of these diseases. It is addressed particularly to the general practitioner, and as the needs of each reader will be different the entire field has been covered in full detail.

Among surgical specialties no advance of the past few years has been more brilliant than that concerned with affections of the lower bowel. The author has presented these advances in full detail, and added a wealth of well considered material from his own unusual experience.

Careful attention is given to the minutiæ in the descriptions of operations and manipulations. Nothing, however trifling, that might make or mar an operation is overlooked. Examination; diagnosis; the preparation of the patient; each step in the operation; the after-treatment; complications that may occur and how to avoid them are all fully presented. The chapters on fistula, constipation, serums and vaccines and sacral anesthesia in particular contain material that will appeal to every man in general practice. The usefulness of this work is enhanced by the clean cut diction of the author; by the modernness of his viewpoint and by the completeness and clearness of the illustrations.

706-8-10 Sansom St.
PHILADELPHIA

LEA & FEBIGER
PUBLISHERS

2 W. 45th Street
NEW YORK

BORDEN'S CONDENSED MILK COMPANY

HAS BEEN AWARDED THE

GRAND PRIZE

HIGHEST AWARD

BY THE SUPERIOR JURY

OF THE

Panama-Pacific International Exp.

AT SAN FRANCISCO

COVERING

Gail Borden Eagle Brand Condensed Milk

Borden's Evaporated Milk **Borden's Malted Milk**

Borden's Condensed Milk Co.

"Leaders of Quality"

Est. 1857 **New York**

NEW (2nd) EDITION **JUST READY** **THOROUGHLY REVISED**

THE PRINCIPLES OF

HUMAN PHYSIOLOGY

By ERNEST H. STARLING, M.D., F.R.C.P., F.R.S.

Jodrell Professor of Physiology in University College, London

Octavo, 1271 pages, with 566 illustrations, 10 in colors. Cloth, $5.00, net.

"The only foundation for rational therapeutics is the proper understanding of the working of the healthy body." About this central idea the author, one of the world's foremost physiologists, has developed his presentation of modern conceptions of human physiology. In the new second edition the developments of recent years have been incorporated, and the whole has been revised to conform to the latest knowledge. This has necessitated the rewriting of the sections dealing with voluntary muscle and with the circulation. Added chapters discuss the nutrition of the brain and the innervation of the bronchi. Emphasis is laid on the significance of the data of physiology and their applications to medicine in order to develop a broad understanding in the student and to make the work most valuable to the physician in his struggle against disease.

706-8-10 Sansom St.
PHILADELPHIA

LEA & FEBIGER
PUBLISHERS

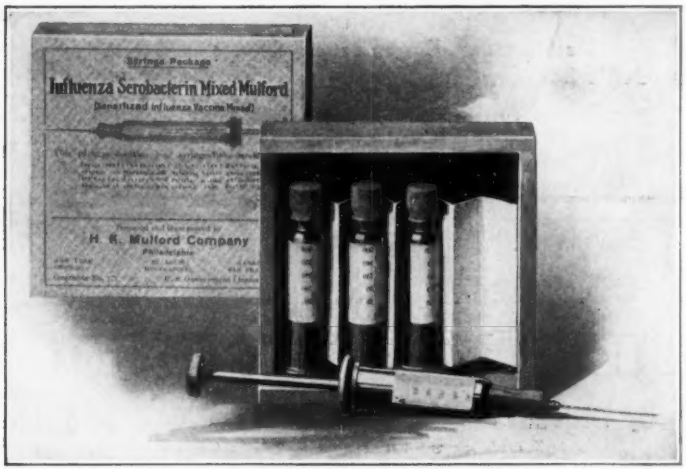
2 W. 45th Street
NEW YORK

Influenza Serobacterin Mixed Mulford

For Immunization Against and Treatment of Influenza and Common Colds

A combination of sensitized killed bacteria prepared from cultures obtained from a large number of patients suffering with acute infections of the respiratory mucous membranes.

Influenza Serobacterin Mixed is employed in catarrhal conditions of the respiratory tract, for treatment and prevention. It may be used either before a cold is fully developed to abort it, during the height of a cold to hasten recovery, or between attacks for prevention.



The usual method of administering Serobacterins is to employ the 4-syringe package, beginning with one-fifth to the entire contents of Syringe A and following with other syringes at two to five-day intervals, according to indications.

Syringes contain killed sensitized bacteria as follows:

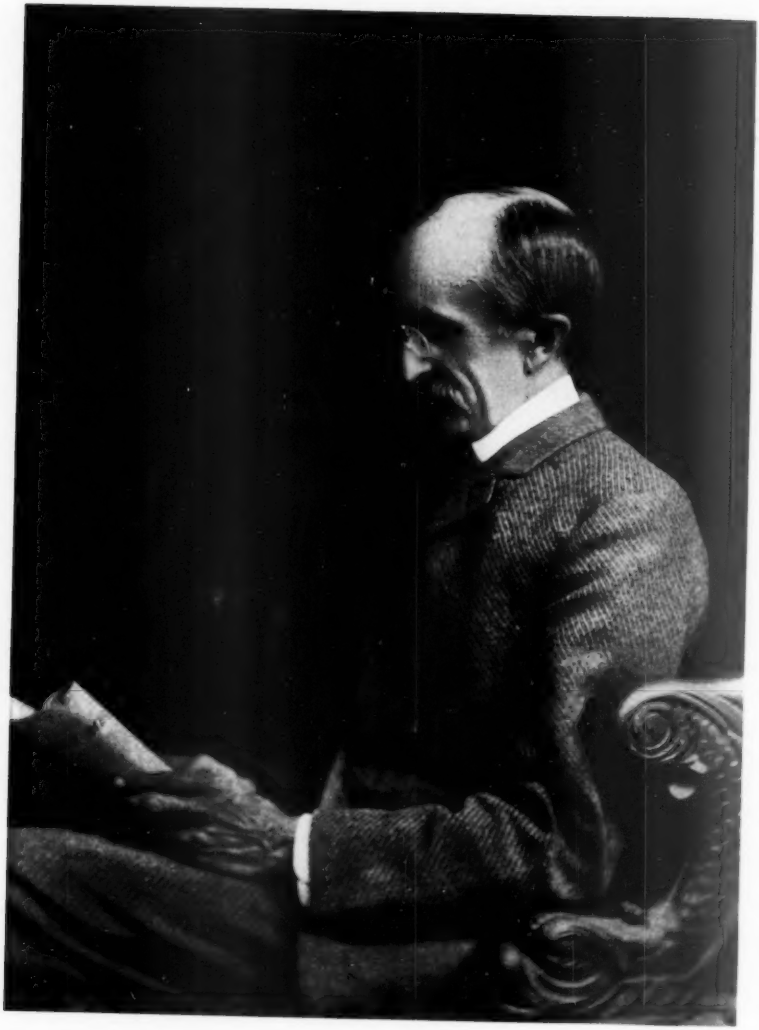
	Syringe A	Syringe B	Syringe C	Syringe D
B. influenzæ	125	250	500	1000 million
Staphylococcus albus and aureus	250	500	1000	2000 million
Streptococcus	125	250	500	1000 million
Pneumococcus	125	250	500	1000 million
M. catarrhalis (group)	125	250	500	1000 million

Literature describing method of treatment and dosage sent on request.

H. K. MULFORD COMPANY

Manufacturing and Biological Chemists

HOME OFFICE AND LABORATORIES, PHILADELPHIA, U. S. A.



E. L. Trudeau

EDWARD LIVINGSTON TRUDEAU, M.D.

I FIRST saw Dr. Trudeau in the summer of 1888, and when I last saw him in the end of August, 1915, scarcely more than two months before his death, I found him surprisingly unchanged in the twenty-seven years that had elapsed. It was in 1872 that he was carried into the Adirondacks—brought there, as he often said, to die. Yet in the forty-three years since then he has done an amount and a quality of work equalled by very few men who call themselves healthy.

In 1888, when I first saw him, he was splendid to look at. His upright, trig, military carriage, his fine, resonant voice, the warmth and beauty of his smile, struck everyone at first glance. These three attributes he preserved even to the end of his life. They were all manifestations of his unquenchable courage. The most remarkable thing about Dr. Trudeau, as I see it, was his stupendous, one might say his supernatural, bravery. Exiled to the Adirondacks in an apparently hopeless stage of tuberculosis, without laboratory instruments, training, or scientific comradeship, he built up the first research laboratory in the country dealing with the problems of tuberculosis. Only those who have tried to do laboratory work alone can appreciate the sort of courage that this needed. Yet he has often spoken of it to me as something done chiefly in self-defense. Without the continuous and secure interest of laboratory work he could not have faced undaunted the task of dealing day after day with hopeless cases of tuberculosis—for at the start of his work he saw very little else. People had not then learned to seek treatment in the more favorable stages of the disease. He always thought of the laboratory as a refuge and solace for himself and other consumptive physicians exiled at Saranac.

Hardly secondary to the stupendous feat of building up this laboratory, which was finally established and given a name in 1894, though he had worked at it long before that by himself, was the feat of starting without money or precedents to guide him, the first

sanatorium for the impecunious consumptive. Though I have put this second in importance, as compared with his laboratory adventure, it was in fact begun in 1884, ten years earlier. That is a long time back in the history of our efforts against tuberculosis in this country. The first State sanatorium for tuberculosis was not opened until 1896, twelve years later. In two great directions of effort, then, scientific and philanthropic, Trudeau was a pioneer. In his prime he was active also in many other directions. When I first knew him he was really the uncrowned King of the Adirondack region, a crack shot, an enthusiastic hunter, interested in every project and every personality in the mountains. No decision of importance could be made without his counsel. Nothing was settled or secure until his judgment had been passed upon it.

Some of us remember how only a few years ago he came down to Washington at the time of the Congress of Physicians and Surgeons to read his memorable address on "Optimism." Optimism from the lips of a man who had everything to discourage and dishearten him is indeed an inspiring gospel. It proved also in his case a potent stimulus to health and vitality. Again and again, when everyone else would have given him up as hopelessly ill, he came back again and again to life and activity, until Dr. Osler came to speak of him as "doing the Phœnix trick once more." Last August, in one of the brief periods of renewed life and activity, he was eagerly planning a postgraduate medical school for the clinical study of tuberculosis at Saranac—he at the end of his forty-three years of struggle against tuberculosis, and less than three months from his death!

It is a great satisfaction to know that he had finished at that time his autobiography, passages of which he then read to me. It is full of his own unique personality, and will preserve for us all one of the most precious and inspiring memories of our lives. To me he is especially inspiring, because his life was throughout built upon a Christian basis. Patients soon came to know that his help was as priceless in the closing hours of life as at any other period. Men needed him to help them live and to help them die. Trusting him first as a man, they came to depend upon his Christian optimism and his Christian hopes.

RICHARD C. CABOT.

THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

DECEMBER, 1915.

ORIGINAL ARTICLES

OBSERVATIONS UPON COMPLEMENT-FIXATION IN THE DIAGNOSIS OF PULMONARY TUBERCULOSIS.[1]

By Charles F. Craig, M.D.,

CAPTAIN, MEDICAL CORPS, U. S. ARMY.

(From the Department Laboratory, Central Department, U. S. Army, Fort Leavenworth, Kansas.)

In the following contribution I shall give the results of certain experiments upon complement-fixation in tuberculosis that have been made in this laboratory during the past year, and that appear to indicate that in this method we possess a valuable aid in the diagnosis of active tuberculous infection and a guide as to the results of therapeutic measures.

The method of applying the test as detailed in this report is not claimed to be perfect by any means, for further research will undoubtedly result in improvements both in technic and results; but as it has given, in my hands, results closely comparable with those obtained with the Wassermann test in syphilis, it is believed that a description of the method is justified. It is hoped that others, who are more favorably situated for work upon this subject may consider the results obtained with this test encouraging enough to warrant further research, and that, as the result of such research, a method will be evolved that will be practical and easy of application, and that will enable us to diagnose tuberculosis in its earliest stages.

[1] Published with authority of the Surgeon-General, United States Army.

HISTORICAL. It would be unprofitable to review here the very numerous attempts that have been made in the past to perfect a method of complement-fixation in tuberculosis that would give uniform and accurate results, and that would be of service in the diagnosis of the disease. Although it was the studies of Wassermann and Bruck upon complement-fixation in tuberculosis that first induced them, together with Neisser, to investigate the possibility of working out such a test in the diagnosis of syphilis, an effort rewarded by the discovery of what is now known as the Wassermann test, up to the present time no method of complement-fixation in the diagnosis of tuberculosis has been generally accepted as of much value by the medical profession.

The researches of Citron appear to demonstrate that after the injection of tuberculin, antibodies are formed capable of binding complement; but the production of these antibodies is transitory, and they soon disappear from the blood serum. Likewise, it has been suggested that during an active tuberculous process complement-binding bodies may be present in the blood serum, but only in small amount, and at varying intervals, while they entirely disappear if the tuberculous process becomes quiescent. Aside from the question of the discovery of a suitable antigen, it has been quite generally held that a complement-fixation test in tuberculosis could never be of practical value because of the variability in the presence of suitable antibodies in the blood serum and in their amount.

However, the consensus of opinion of late appears to be that with a suitable antigen one should be able to devise a complement-fixation test for tuberculosis that would give useful results. This opinion has lead to the study of antigens that might be used in such a test, and for this purpose various substances have been used, as watery and alcoholic extracts of tuberculous organs, either alone or combined with some form of tuberculin; tuberculin alone; tuberculin filtrate; watery extracts or emulsions of the tubercle bacillus; and mixtures of various tuberculins. With the exception of the antigens described by Besredka and by Hammer, no very practical results have been obtained with any of those mentioned.

The antigen recommended by Besredka,[2] consisting of a suspension of bacterial substance derived from dried and ground tubercle bacilli, and that of Hammer,[3] consisting of an alcoholic extract of tuberculous tissue to which has been added a certain amount of old tuberculin, appear to have given very consistent results; but, unfortunately, reactions have occurred with these antigens in other conditions, especially in syphilis, and in a considerable proportion of the cases tested.

[2] Compt. rend. Soc. de biol., 1914, lxxvi, 180.
[3] Münch. med. Wchnschr., 1912, lix, 1750.

In a recent very valuable study by Bronfenbrenner[4] the results are given of experiments made with the antigen of Besredka in the diagnosis, by complement-fixation, of tuberculosis. He found that in active tuberculosis he obtained 93.8 per cent. of positive reactions; in convalescents presenting no symptoms of the disease, 55.5 per cent. of positive results; while in cases strongly suspected of tuberculosis but in which no definite diagnosis has been made, 75 per cent. gave a positive reaction. However, in treated and untreated cases of syphilis he obtained 24 per cent. of positive reactions with this antigen and 8 per cent. of his controls reacted positively. He found that he could separate from Besredka's antigen the substance or substances giving positive reactions with syphilis and other conditions, and that this purified antigen apparently was specific for tuberculosis. In regard to certain negative reactions obtained in undoubted active tuberculosis he states that they suggest that in certain stages of the infection the circulating antibodies apparently disappear from the blood.

Several other investigators have reported very favorable results with Besredka's antigen, notably Inman,[5] who obtained 95 positive reactions in 100 cases of active tuberculosis; and while these reports are very encouraging, the large percentage of syphilitics that react positively with this antigen militates against its use as a diagnostic agent. On the other hand, the method described in this paper does not possess this disadvantage, for the antigen employed does not give positive results with the blood serum of syphilitics in the absence of coincident tuberculous infection.

Technic and Material. The general technic of the complement-fixation test for tuberculosis experimented with is that employed in making the Wassermann test in this laboratory, and which I have described fully in previous contributions.[6 7 8]

The *antigen* employed consists of an extract of several strains of the human tubercle bacillus, prepared as follows: The various strains of the bacilli are grown on a liquid medium composed of alkaline bouillon to which a teaspoonful of egg white and egg yolk has been added to each 250 c.c. of the bouillon. After growth is well advanced, an equal amount of 95 per cent. alcohol is added to the culture, and the whole shaken in a shaking machine for twelve hours; the mixture is then allowed to stand in an incubator at 37° C. for twenty-four hours, after which it is again shaken for six hours and filtered through a very fine filter paper or through a Berkefeld or other equally good filter. It appears to make no difference

[4] Arch. Int. Med., 1914, xiv, 786.
[5] Compt. rend. Soc. de biol., 1914, lxxvi, 251.
[6] Craig, C. F., Jour. Exper. Med., 1910, xii, 726.
[7] Craig, C. F., Jour. Infect. Dis., 1911, ix, 213.
[8] Craig, C. F., and Nichols, H. J., Studies of Syphilis, Bull. No. 3, War Dept., Office Surg.-General of Army, 1913, lxxii.

whether the mixture be filtered through a paper or through the Berkefeld so far as antigenic properties are concerned. The filtrates of the strains cultivated are mixed together and the resultant mixture titrated for anticomplementary, hemolytic, and antigenic qualities. The undiluted mixture should be titrated first, as in my experience it is seldom necessary to dilute the mixture.

An antigen may also be prepared by carefully transferring a portion of all of the strains used to a large culture flask, planting each strain far enough apart so that it may be observed whether growth occurs. Generally one or more of the strains transplanted in this manner fail to grow, but this can be disregarded if one works with eight or more strains. When growth has occurred to a considerable extent the alcohol is added, as already described, and the antigen prepared in a similar manner. Antigens made in this way appear to be slightly stronger in antigenic content than when the filtrates of the separately cultivated strains are mixed, but the greater difficulty of cultivating so many strains of the bacillus together more than offsets the slight gain in complement-binding power.

The antigen must be kept in the ice-box except when a small portion is removed for use in the test, as exposure to room temperature, even for a short time, markedly lessens its antigenic properties. It is also necessary that the greatest care be taken that all utensils used in the preparation of the antigen are sterile.

The preparation of a polyvalent antigen for use in this test was suggested by the fact that there are modifications of both the human and bovine types of tubercle bacilli and that some strains of the organisms differ from others in infective power and in cultural reactions. It is probable, indeed, that by adding strains of the bovine bacillus to the antigen, better results will be obtained than when the human strains alone are used, and this subject is now being investigated. It is also believed that a polyvalent antigen prepared by extracting the various strains of the bacillus grown upon solid media, using only the bacterial growth, will probably prove as accurate as the antigen described, and, if, so, it will greatly simplify the method of making the antigen.

A human *hemolytic* system was employed in the test, the amboceptor being obtained by injecting rabbits with human red-blood corpuscles in the usual manner, and the *blood suspension* used consisted of a 1 per cent. suspension of human red-blood corpuscles in normal saline solution. As *complement* guinea-pig blood serum was employed, and this was invariably titrated just before use. The blood sera tested were inactivated at 56° C. for one-half hour before testing, and the final reading of the test was generally made an hour after taking the specimens from the water-bath.

The methods of preparing and titrating the various reagents and the technic of performing the test were the same as in the

Wassermann test as made in this laboratory, and have been fully described elsewhere.[9]

Material. Through the kindly assistance of Colonel Bushnell, Medical Corps, U. S. Army, commanding the U. S. Army General Hospital at Fort Bayard, and Lieutenant Callender, who collected the specimens, I was able to test the blood of 166 patients in that institution suffering from pulmonary tuberculosis. In addition, the blood of 150 syphilitics as well as of 100 patients suffering from other diseases was tested, and also 150 normal individuals who were used as controls.

Method of Reading the Results of the Test. The final result of the test was read from an hour to two hours after the last incubation in the water-bath, and this is important, as otherwise some of the positive reactions may become weak or negative. If left in the ice-box over night many of the strongest positive reactions are negative in the morning. Accurate results can only be obtained by reading the test within the time specified.

Early in the work it was determined to estimate the strength of the reaction in tuberculosis in the same manner as the Wassermann test in syphilis, in which the results have been recorded as double-plus (++); plus (+); plus-minus (±); and minus or negative (−). When complete inhibition of hemolysis is obtained the result is recorded as double-plus; when less than 50 per cent. of the blood corpuscles are hemolyzed, as plus; when more than 50 per cent. are hemolyzed, as plus-minus; and if complete hemolysis occurred as minus, or negative. However, it was quickly found that many cases of tuberculosis gave very strong plus reactions, so that it early became evident that a plus reaction with this test was diagnostic of tuberculosis, as it did not occur in other diseases or in healthy individuals. On the other hand it was also found that a plus-minus reaction sometimes occurred both in other diseases and in normal individuals, so that this type of reaction had to be considered as practically negative. In considering the results of the test as here given it should be understood that a positive result includes both double-plus and plus reactions, while a negative includes both plus-minus and minus reactions.

As regards the relative number of double-plus and plus reactions it may be stated that of the 142 cases of pulmonary tuberculosis that reacted to the test, 119 gave a double-plus reaction and 23 a plus reaction; of the 103 cases of active infection reacting, 87 gave a double-plus reaction and 16 a plus reaction; while of the 39 inactive cases of infection, 32 gave a double-plus reaction and 7 a plus reaction. Owing to the percentage of tuberculous cases giving a plus reaction, the test as at present developed requires very careful titra-

[9] Craig, C. F., and Nichols, H. J., Studies of Syphilis, Bull. No. 3, War Dept., Office Surg.-General of Army, 1913, lxxii.

tion of all the reagents and experience in reading the results of hemolytic reactions.

The tests made in this laboratory in the study of this subject may be divided into three groups, as follows: Group 1. Cases in which the diagnosis was pulmonary tuberculosis, either active or inactive. Group 2. Cases in which the diagnosis was of some other disease. Group 3. Normal individuals.

Results of the Test in Group 1. In order to understand the results of the complement-fixation test and their significance in this group it is necessary to briefly describe the classification of the cases tested, which is that followed at the U. S. Army General Hospital at Fort Bayard, New Mexico.

The cases tested were divided into three general classes: Class 1, including incipient cases of tuberculosis; Class 2, moderately advanced cases; and Class 3, far-advanced cases. In addition the cases were classified as *active* and *inactive*, and, again, with reference to the extent of the involvement of lung tissue as *Involvement 1*, indicating a slight lesion extending at most to the volume of one lobe or two half-lobes; *Involvement 2*, slight lesion extending further than *1*, but at most to the volume of two lobes or a severe lesion extending at most to the volume of one lobe; and *Involvement 3* including all lesions which in extent of the parts affected exceeded *Involvement 2*.

The total number of cases of pulmonary tuberculosis tested was 166, of which 142, or 85.5 per cent., gave positive results, and 24, or 14.4 per cent., gave negative results.

The cases were divided as regards the nature of the infection into *active* and *inactive* infections, and the following table gives the results of the test in each class:

TABLE I.—RESULTS OF THE COMPLEMENT-FIXATION TEST IN PULMONARY TUBERCULOSIS WITH REFERENCE TO THE ACTIVITY OF THE INFECTION.

Total cases.	Active.	Inactive.	Positive.	Per cent.	Negative.	Per cent.
166	107	..	103	96.2	4	3.7
	...	59	39	66.1	20	33.8
	107	59	142	85.5	24	14.4

From the foregoing table it is evident that the percentage of positive results obtained with this test in active tuberculous infection was much higher than in the cases classed as inactive, 96.2 per cent. of the active cases giving positive results, while only 66.1 per cent. of the inactive cases reacted to the test. It should be remembered that the classification into active and inactive cases is entirely clinical, and that many of the cases giving a positive result in the inactive class were merely quiescent and may or may not have shown the bacilli in the sputum.

The percentage of positive results in active tuberculous infection of the lungs, *i. e.*, 96.2 per cent., is as high as that obtained in my experience with the Wassermann test in secondary syphilis, for in 1969 cases in that stage of the disease I have obtained positive reactions in 96.1 per cent. of the cases. This speaks very favorably for the accuracy of this test in the diagnosis of active tuberculous infection, and indicates that in this class of cases we may expect as good results with it as are obtained with the Wassermann test in secondary syphilis.

The percentage of positive results in clinically inactive tuberculous infection is practically the same as that I have obtained in latent syphilis with the Wassermann test. In the clinically inactive cases of tuberculosis, 66.1 per cent. gave a positive reaction, while in 1354 cases of latent syphilis I have obtained 69.4 per cent. of positive results.

The importance of the comparatively large percentage of positive results in clinically inactive tuberculosis consists in the demonstration of the fact that the infection in these cases was not really inactive, if we believe that complement-fixing bodies in the blood indicate an activity of the infection. In the past it has been generally accepted that such bodies were not demonstrable in the blood serum unless tuberculosis was clinically active; but the results of this test prove that such bodies can be demonstrated when the disease is inactive clinically. For this reason it would appear that a positive reaction indicates an active focus somewhere in the body and that the test will prove of value in differentiating really cured infections from those which are simply quiescent.

Relation of the Results to Class of Patients Tested. It has been stated that the cases of pulmonary tuberculosis tested were divided into three classes: incipient cases, advanced cases, and far-advanced cases. It was found, as would be expected, that the highest percentage of positive results was obtained in patients in whom the infection was furthest advanced, as is shown in the following table:

TABLE II.—COMPLEMENT-FIXATION IN TUBERCULOSIS IN RELATION TO THE CLASS OF INFECTION.

Class.	Character of infection		Positive reaction.	Per cent. positive.	Negative reaction	Per cent. negative.
	Active.	Inactive.				
1. Incipient cases	1	..	1	100.0	0	0.0
	..	24	14	58.3	10	41.6
Total, 25	1	24	15	60.0	10	40.0
2. Moderately advanced cases	53	..	51	96.2	2	3.7
	..	32	22	68.7	10	31.2
Total, 85	53	32	73	85.8	12	14.1
3. Far advanced cases	53	..	51	96.2	2	3.7
	..	3	3	100.0	0	0.0
Total, 56	53	3	54	96.4	2	3.5

While in the foregoing table the percentage of positive results happens to be the same for active infections in both moderately advanced and far-advanced cases, in the inactive infections the positive percentage is much greater in the far-advanced cases, and in the incipient cases the percentage of negative results is higher than in either the moderately advanced or far-advanced infections.

The relation of the results of the complement-fixation test to the amount of lung involvement is shown in Table III, where the infections are arranged in accordance with the amount of involvement, as previously defined.

TABLE III. — COMPLEMENT-FIXATION IN PULMONARY TUBERCULOSIS IN RELATION TO THE AMOUNT OF LUNG INVOLVEMENT.

Nature of infection.	Involvement.			Positive reaction.	Per cent. positive.	Negative reaction.	Per cent. negative.
	1	2	3				
Active	29	..	..	27	93.1	2	6.8
	..	30	..	30	100.0	0	0.0
	..	..	48	46	95.8	2	4.1
Total, 107	..	..	..	103	96.2	4	3.7
Inactive	43	..	..	27	62.7	16	37.2
	..	14	..	10	71.4	4	28.5
	..	..	2	2	100.0	0	0.0
Total, 59	..	..	..	39	66.1	20	33.8

In general, it will be noted that the greater the amount of lung involvement the greater the percentage of positive reactions, both in the active and inactive infections, and while it may be objected that the number of cases tested is small, I believe that further research will confirm these results.

Results of the Test in Group 2. This group, as stated, included all cases in which the clinical diagnosis was of some disease other than tuberculosis. In all, 250 individuals were tested, of whom 150 were suffering from syphilis and 100 from other diseases, including both acute and chronic conditions.

Of the total number examined, two gave a positive reaction with the test, or 0.8 of 1 per cent. In both positive cases the patients were syphilitic and gave a positive Wassermann reaction; but careful examination revealed lesions of the lungs suggestive of tuberculosis, although no bacilli were demonstrated in the sputum.

That the positive reactions obtained in these two cases giving a positive Wassermann reaction were not due to the syphilitic infection is proved by the fact that of 150 syphilitics tested, all giving a positive Wassermann, not one gave a positive reaction with the antigen employed in the complement-fixation test for tuberculosis here described, a result strongly in contrast with that obtained when Besredka's antigen is used, for with the latter antigen Bronfenbrenner obtained nearly 24 per cent. of positive results in syphilitics in

whom tuberculosis was not suspected. He states, however, that 5 of the cases included in this percentage have since developed symptoms of tuberculosis, which reduces the percentage of positive results in syphilis to 17 per cent.

Of the patients suffering from other diseases, 100 in number, all gave a negative reaction with the test described in this paper, and while the number of cases is comparatively small, their great variety and the uniformly negative results obtained demonstrate, I believe, that this test will not react positively with diseases other than tuberculosis, nor with the blood serum in cases where a tuberculous infection has become encapsulated, for among this number of individuals there must have been many who had encapsulated tuberculous lesions and who would have given a positive reaction with the tuberculin tests.

Results in Group 3. The blood serum of 150 individuals in good health and free from tuberculous infection, so far as could be ascertained, was tested and a negative result was obtained in every instance. While these tests were made upon young, healthy soldiers, I am very sure that had any of the tuberculin tests been applied to the same individuals a considerable proportion of positive results would have been obtained if our conceptions regarding the percentage of individuals who have inactive tuberculous lesions are correct. The fact that the complement-fixation test in so many individuals was negative, speaks strongly in favor of its being a specific test for active tuberculous infection, and indicates that it will not give positive reactions in inactive cases or where the lesions have become encapsulated.

Discussion of Results. I believe that the experiments recorded in this contribution indicate that a complement-fixation test for tuberculosis, capable of giving as good results in the diagnosis and the control of the treatment of the disease as does the Wassermann test in syphilis, can be evolved, and that the test here described approaches very nearly this ideal. While it is unfortunate that so few cases of tuberculosis in the incipient stage could be tested, for it is in this stage of the disease that the test would be of greatest value in diagnosis, the fact that 60 per cent. of the cases that were tested in the incipient stage gave a positive reaction, although all were recorded as inactive clinically, speaks eloquently for the accuracy of the test in the diagnosis of early cases.

The results of the test also demonstrate that while a patient may have a clinically inactive tuberculous infection, the blood often gives a positive complement-fixation reaction, and this fact should prove of considerable value in the control of the treatment of the disease. While it would be premature to argue that a negative complement-fixation reaction in clinically inactive cases of tuberculosis means that the infection is cured, it is quite evident that in many cases proved to be inactive clinically a positive reaction *is*

obtained, and this certainly would appear to indicate that there is still an active focus present, although no symptoms can be detected. On the other hand, where a negative reaction is repeatedly obtained and no symptoms indicating the presence of an active infection are present, it would appear to be reasonable to conclude that the infection has disappeared. However this may be, I am forced to conclude, as the result of these experiments, that a positive result with the complement-fixation test described, indicates the presence of an active tuberculous infection, even though the disease may be clinically inactive, and that as long as the test remains positive the patient cannot be said to be cured. This conclusion is based upon the uniformly negative results of the test in healthy individuals, the large percentage of positive results obtained in active tuberculosis, and the comparatively large percentage of positive results in clinically inactive cases of the disease.

The strength of the reaction has been found to vary from day to day in some cases, a strongly positive reaction alternating with a plus-minus or even a negative reaction. This variation in the strength of the reaction I have shown to[10] be true of the complement-fixation test in syphilis; and more recently, Irons and Nicolls[11] have shown the same to be true of complement-fixation in gonorrheal infections. Therefore, in this test, as in complement-fixation in the other diseases mentioned, a single negative reaction is of no value in excluding infection. Repeated tests should be made in all cases in which tuberculosis is suspected, and a negative report should not be made until several tests have been performed.

Conclusions. The following conclusions appear to be justified from the results of the complement-fixation test for tuberculosis reported in this paper:

1. Complement-binding antibodies are present in the blood serum of both active and clinically inactive tuberculous infections.

2. A polyvalent antigen prepared from several strains of the human tubercle bacillus has been found to give excellent results in complement-fixation for tuberculosis.

3. With the test described, complement-fixation gave a positive reaction in 96.2 per cent. of cases of active tuberculosis and in 66.1 per cent. of the cases of clinically inactive tuberculosis.

4. The test was negative in normal individuals and in patients suffering from other diseases with the exception of two patients infected with syphilis in whom symptoms of a coincident tuberculous infection was also present.

5. The test does not give positive results with the blood serum of syphilitics in whom there is no coincident tuberculous infection.

6. The reaction, when positive, is specific and apparently indicates.

[10] Craig, C. F., Jour. Amer. Med. Assn., 1914, lxii, 1232.
[11] Jour. Infect. Dis., 1915, xvi, 303.

the presence of an active tuberculous focus, although there may be no symptoms of the disease present.

7. Positive results are obtained in a large percentage (66 per cent.) of clinically inactive cases of pulmonary tuberculosis, and such a result indicates that though it may be quiescent the infection has not disappeared.

8. The results obtained with the test described are practically as good as those obtained with the Wassermann test for syphilis.

Of course, much more work is needed before this, or any other method of diagnosing tuberculosis by complement-fixation is placed upon a thoroughly practical basis and is generally accepted as a routine diagnostic measure, but it is confidently believed that continued work upon this subject will result eventually in the perfection of a test that will be fully as useful in the diagnosis and control of the treatment of tuberculosis as is the Wassermann test in syphilis.

I desire here to express my thanks to Doctor Edward R. Baldwin for seven strains of the human tubercle bacillus kindly furnished me from the Saranac Lake Laboratory, and to Dr. Simon Flexner for three strains of the bacillus from the Rockefeller Institute. The antigens used in my experiments were prepared from six of the strains furnished by Dr. Baldwin and one of the strains furnished by Dr. Flexner.

LANDRY'S PARALYSIS: REPORT OF A CASE WITH NECROPSY AND HISTOPATHOLOGICAL FINDINGS.[1]

By Edward D. Fisher, M.D.,
NEW YORK.

Many cases have been reported since Landry first described a disease characterized by a rapidly ascending paralysis passing from the lower to the upper extremities, thence to the cranial nerves, causing various paralyses, and ending fatally in the course of six or seven days with involvement of the vagus and respiratory failure. The pathological changes in the early cases were negative. This may have been due to the insufficient method of examination in part, but even in later reports very few changes have been found at times.

In the literature of this subject, which is considerable since Landry, in 1859, described his case, we find various lesions recorded in which either polyneuritis or spinal cord or bulbar inflammatory involvement has been present, or all in combination. Leyden and

[1] Read before the Americal Neurological Society, New York City, May 8, 1915.

Goldscheider are among those who support this view. The cord changes are usually hyperemia, perivascular and pericellular infiltration, and hemorrhages into the gray and white matter; at times an interstitial and parenchymatous neuritis with or without cell involvement in the cord and bulb. The latter type is rather the exception than the rule. Our case belongs to the neuritic type with involvement of cells of the cord and brain stem.

E. Lugaro made an exhaustive study of reported cases of Landry's paralysis of the neuritic type up to 1904. He prefers to designate Landry's paralysis as a clinical entity characterized by an acute ascending flaccid paralysis, irrespective of pathological findings. And he cites cases of a purely neuritic type of Centanni, Eisenlohr, Leyden, Thomas, Reusz, Krewer, Wochenius, Roth, Rosenheim, Nauwerk, and Barth. All of their cases presented the same syndrome, namely, an acute ascending flaccid paralysis. Besides the interstitial and parenchymatous neuritis, there were also cell changes in the anterior and posterior horns of the cord. But these were of a reactionary type, due to remote influences in their neuraxones.

All authors agree that the disease is of infectious origin, and attempts have been made to isolate a specific organism, but without success. Centanni isolated a bacillus from the nerve trunks, Eisenlohr a Staphylococcus pyogenes and a Staphylococcus cereus albus from the spleen and sciatic nerve. Leyden's case came on after influenza. Wochenius found a Staphylococcus pyogenes albus in the spleen and peripheral nerves. In some cases pulmonary tuberculosis was a complication. Lugaro goes so far as to classify the cases reported by Korsakow and Serbski as puerperal polyneuritis, and similar ones reported by Prybitkow and one by Mader, as Landry's paralysis, because of the clinical picture.

Because of the fact that there is no specific agent causing the affection, he is inclined to advance the hypothesis that the toxin alone is responsible for the extensive destructive changes in the nerve tissues, and that in some cases only both the virus and its toxin are at work. He also points out that the time element as to the duration of the disease is not material for it may last a few days or a few weeks.

Since 1904 several other cases were reported that approximate my case both as to clinical and pathological data. Among them Pfeiffer, Burghart, Mosny and Moutier, and others report such types. The cases of Burghart and of Mosny and Moutier were complicated by pulmonary tuberculosis and lasted four weeks and two months respectively. In none of these cases was any germ isolated. Levaditti has injected a monkey with the emulsion of the cord of Moutier's case, and obtained negative results.

The case I shall record may be of interest, as it was observed from the onset, and a careful postmortem examination has been made.

CASE REPORT. W. E., boy, aged fifteen years. Family history is negative. With the exception that he was operated upon for an inguinal hernia two years before his present illness, his personal history is negative.

Present Illness. September 27, 1913, he complained of a sharp pain in the calf of the left leg. This pain was gone the next day, but left him with a weakness in both lower extremities. He was able to walk without much difficulty but favored his left leg, holding it somewhat bent to keep him from falling. This condition grew progressively worse until October 11, when he was admitted to St. Vincent's Hospital, in the service of Dr. Constantine J. MacGuire. His paraplegia was then complete and he had to be carried to the hospital.

Status on Admission to the Hospital. Patient was well developed and a little above the average height for his age. The temperature was 99.2°, pulse 72, and respirations 24.

Examination of heart, lungs, and abdominal viscera was negative.

Muscles of the head and neck and of upper extremities were normally active. There was a flaccid paralysis of the lower extremities, with loss of reflexes and pain on pressure over the large nerve trunks. There was no dissociation of touch, pain, or temperature sense. No anesthesia. Deep muscle sense was normal.

Laboratory Findings. Urine, amber color; acid; specific gravity, 1019; albumin and glucose negative; no casts; no crystals. Blood: leukocytes, 23,500 per cubic millimeter; polynuclears, 86 per cent.; transitionals, 2 per cent.; lymphocytes, 12 per cent. Spinal fluid clear and colorless; normal pressure. Fehling's reduction test positive; globulin slightly increased and 7 cells per cubic millimeter. Smears and cultures negative for bacteria. Wassermann reaction negative in blood serum and spinal fluid. Throat cultures negative.

October 15. Patient vomited and complained of severe abdominal pain and chilly sensations. Blood culture taken and proved negative. The pain and vomiting were relieved by catharsis and colonic irrigation.

October 17. Complains of seeing double and holds the left eye closed so as to prevent it. Paralysis of left external rectus. Dr. Kelly examined the eye-grounds and found them to be negative.

October 25. Restless the greater part of the night and complains of pain in the left shoulder. Has a headache and vertigo and vomited after lunch. From this time he had a progressive weakness and loss of power in arms and hands, until in about one week it was complete.

October 29. Headache is gone, but complains for the first time of some difficulty in swallowing. Dr. Kelly reports now complete paralysis of the muscles of the right eye and of the superior oblique of the left.

November 1. Blood count: leukocytes, 5900; polynuclears, 60 per cent.; lymphocytes, 38 per cent.; basophiles, 2 per cent.

November 3. Complains of pain in the cardiac region.

November 9. Again had difficulty in swallowing, and had pain in the back and temporary shortness of breath.

Neurological Examination. Cranial nerves: I, unaffected; II, negative; III, left normal; almost complete right-sided palsy; right ptosis; pupils react to light and accommodation well; IV, left paralyzed; V, right affected; diminished sensation of cornea and right side of face; weakness of masseter; VI, left paralyzed; VII, bilateral facial paralysis of the peripheral type; unable to wrinkle forehead, show teeth or close eyes tightly; difficulty in pronouncing consonants "b" and "p"; VIII, IX, and X, normal; XI, affected; trapezii and sternomastoids weakened; XII, normal. Motor functions: double foot-drop with complete loss of power in legs, flexors, and extensors being equally involved. Double wrist-drop. With the exception of slight movements of fingers, almost complete paralysis of upper extremities. Muscles of trunk markedly involved.

Sensory functions: Coördination, deep muscle sense normal. Decreased touch and temperature sense.

Trophic disturbances: Marked atrophy of muscles of lower extremities. Slight atrophy of muscles of arms and hands.

Reflexes: K. J., A. K., W. K., E. K., absent. Abdominals present. Pupillary normal. Sphincters normal.

Electrical reactions: Absence of faradic response and R. D. present in lower, quantitative and qualitative diminution in upper extremities.

November 17. Marked shortness of breath, respirations 40, almost wholly costal. Pulse, 90. First valvular sound impure, second pulmonic accentuated. Pulmotor had to be used to relieve dyspnea. Pulse went up to 150, and was weak and thready.

November 21. Patient died of respiratory failure.

Necropsy. Dr. John H. Larkin made the autopsy and reported that the thoracic and abdominal viscera were normal. The cord showed an intense congestion, but otherwise was macroscopically negative. Sections of the sciatic nerve, cord, medulla, and pons were prepared by him and studied by Dr. M. Neustaedter, who makes the following report on the histopathology of the case:

Microscopic Study. Sections of all levels of cord, medulla, pons, and the sciatic nerve were examined. These were stained according to the methods of Nissl: toluidin blue and polychrome methylene blue; Van Gieson, Mallory, Bielschowski, Weigert-Pal, Nigrosin stain; Marchi and Sudan III.

Spinal Cord. Sections from the lumbar, dorsal, and cervical segments. The cells of Clarke's column show a central chromatolysis, with remnants of small, narrow, and poorly defined and

darkly staining bodies lining the periphery of the cells. The protoplasm of the remaining cell is a diffused granular mass assuming a faint stain and giving the cell a dusty appearance. The cells are markedly swollen, and nuclei, when present, are eccentrically situated. The nucleoli stain rather darkly and under high magnification show a disintegration of their substance into bodies of various shapes and sizes. The cell prolongations are everywhere faintly stained. This degeneration is manifested in all the cells

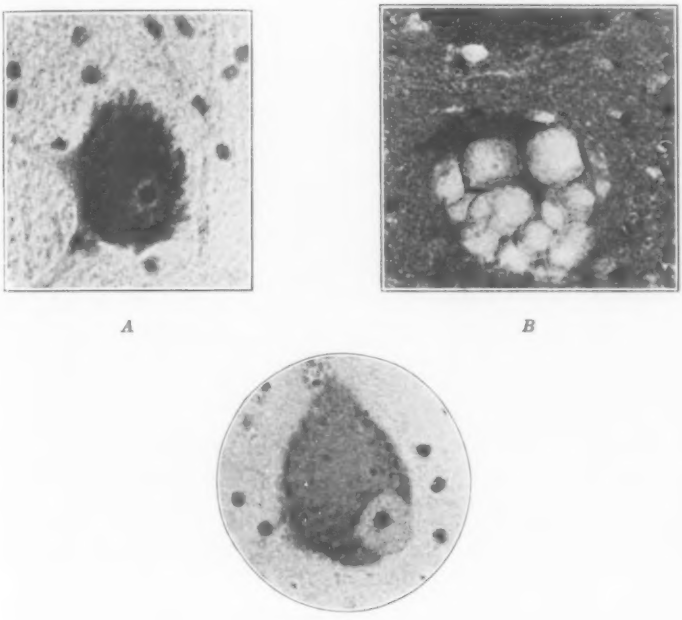


FIG. 1.—*A*, degeneration of anterior horn cells, showing a tygriosis and a beginning chromatolysis around the periphery, with eccentric nucleus. Nissl stain. Zeiss, 8 mm. Oc. 6. × 450. *B*, cell vacuolization of anterior horn cell. Van Gieson stain. *C*, degeneration of cells of Clarke's column, with central chromatolysis, chromophilic substance lining the periphery. Nissl stain. Zeiss, 16 mm. Oc. 3. × 60.

of Clarke's column at all levels of the cord. Nowhere along this column is any evidence of a neuronophagocytosis to be found, although there is a fair amount of hyperplasia of glia cells in their vicinity.

The large multipolar cells of the anterior horns throughout all the segments of the cord are seen to have undergone three forms of degeneration of various intensities. The most prominent feature is a coalescence of the tygroid substance, a tygriosis, and a con-

sequent shrinkage. The cells stain darkly or assume such an intense stain that the chromophilic substance cannot be differentiated at all. This condition cannot be an artifact or overstaining, since other cells on the same section are staining quite well. In assuming such a dark stain the cell obliterates the view of the nucleus if present. In some cells the nucleus is eccentric and its cytoplasm broken up into irregular bodies and the nucleolus is staining very deeply. The prolongations of these cells are visible and retain slight meshes of chromophilic substance. Around the periphery of the cells and at times dipping into the cell body itself are seen round cells, large and small, of the type of satellite cells. To a lesser extent we find cells in the anterior horns, with a central

FIG. 2.—A diffuse and focal infiltration of leukocytes in the anterior nerve root, cervical segment. Nissl stain. Zeiss, 16 mm. Oc. 3. × 150.

chromatolysis of the type described in the cells of Clarke's column. In cells affected by this phase of degeneration the prolongations are gone and no evidence of any neuronophagocytosis is present. Very rarely, indeed I have only seen it on three sections, there appears to be a cell vacuolization with the nucleus entirely gone and a slight neuronophagocytosis present. The first type of degeneration is most pronounced in the anterior horns of all the cervical and dorsal segments, while the second type is most pronounced in the anterior horns of all levels of the lumbar region and in the cells of the lateral horns all over the cord.

The significance of these phases of cell degeneration has been established by pathological investigation and experimentation,

namely, that a central chromatolysis with swelling and eccentricity of the nucleus, together with chromophilic substance present in well-defined meshes around the periphery of the cell, is accepted to be a reactionary degeneration or attempted regeneration of the cell as a result of a lesion remotely in the cell prolongation—in the neuraxone. While the degeneration beginning as a tygriosis, coalescence of the chromophilic substance accompanied by swelling in some instances, and a shrinkage or cell vacuolization following it in the presence of a more or less marked neuronophagocytosis and a gradual cell destruction in which the tygroid substance is present

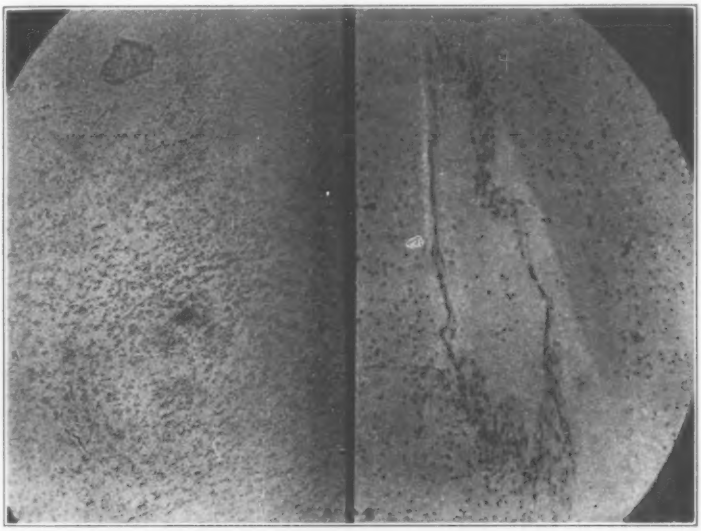


FIG. 3.—*A*, focus of marked glia-cell proliferation in the gray matter in the neighborhood of the aqueduct on a section through the red nuclei. Nissl stain. Zeiss, 16 mm. Oc. 3. × 60. *B*, slight perivascular infiltration of mononuclears in the same neighborhood. Nissl stain. Zeiss, same magnification as *A*.

as long as a part of the cell is present is accepted as an inflammatory reaction within the cell itself, or its pericellular lymph space or in the substance of its immediate neighborhood. In the first type we see slight evidence of any remaining neuraxone or other cell prolongation, while in the latter type we always see a well-stained cell prolongation with some meshes of the chromophilic substances.

In view of the fact that we have the first type of cell degeneration present to a great extent, and the second type only in some parts of the anterior horns, we should expect definite pathological changes in the peripheral nerves and a clinical picture in conformity with

these. This discussion we shall leave to the end after first reporting the other findings.

Sections stained by the Bielschowski method show a marked degeneration of the neurofibrils of the cells of the anterior horn, while those of the cells of Clarke's column are entirely absent. This is true of all the levels of the cord.

There is a considerable hyperplasia of glia cells in the gray and white matter of the whole cord, and not infrequently do we meet with darkly staining, small mononuclear round cells, especially pro-

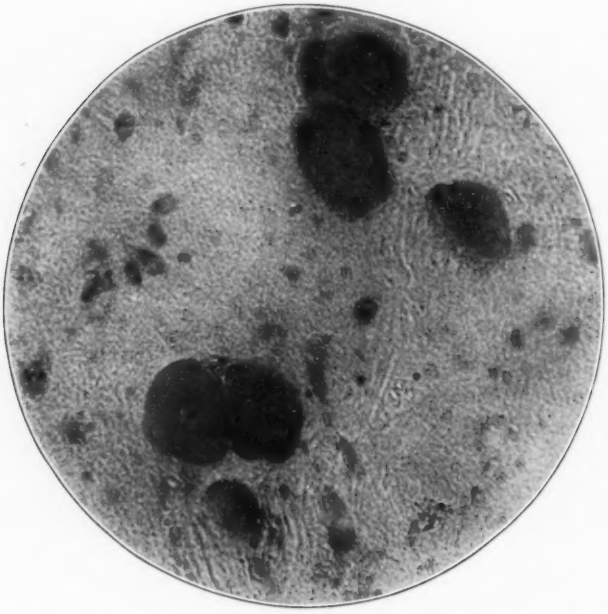


FIG. 4.—Swelling, central chromatolysis, and degeneration of the cells of the descending nucleus of the fifth. Nissl stain. Zeiss, 8 mm. Oc. 6. × 440.

nounced in the neighborhood of the blood vessels, filling in their perivascular sheaths to a very slight extent. They are most probably lymphocytes.

A feature of considerable interest in this case is the ependymitis around the central canal, especially well established at the levels of the cervical and lumbar enlargements. We find here a considerable hyperplasia of ependymal cells with an intense infiltration of large polymorphonuclears around the central canal with not an inconsiderable amount of small, darkly staining mononuclears. At

some levels of the cervical enlargement there are even some large polymorphonuclears found within the lumen of the canal.

Finally, it must be noted that the capillaries of the gray matter of the anterior horns are engorged. In many instances one notices capillary aneurysms, and not infrequently these burst and give rise to extensive hemorrhages. Hemorrhages of the white matter I have noticed only in a few instances in the posterior columns.

The Medulla and Pons. The cells of the nuclei graciles and cuneati show a pronounced degeneration of the type found in the cells in Clarke's column of the cord, while the cells of the motor nuclei and of the formatio reticularis show evidences of the type

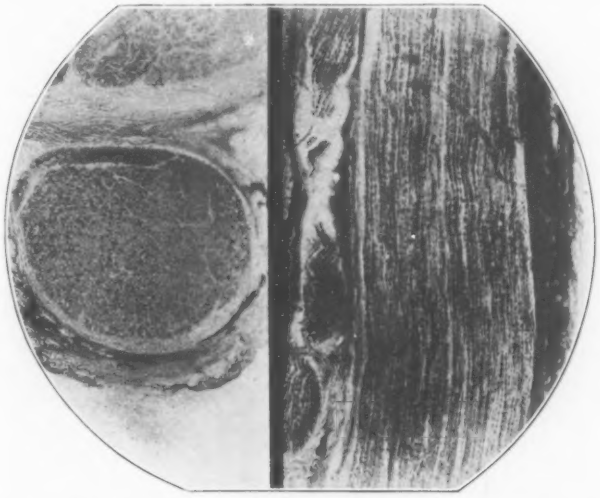


FIG. 5.—Longitudinal and cross-sections of the sciatic nerve, showing pronounced degeneration of the myelin substance. Marchi and Weigert-Pal stains. Zeiss, 16 mm. Oc. 3. × 60.

of degeneration we found in the ganglion cells of the anterior horns of the cord, namely, a tygriosis. Throughout the segment at the level of the decussation of the pyramids there is a fair amount of hyperplasia of glia cells and some diffuse and very slight perivascular infiltration of deeply staining, small, round mononuclears. The central canal shows here also some ependymitis as in the cord.

The cells of the nuclei of the third and sixth cranial nerves show the following form of degeneration. There is a central chromatolysis around the nucleus, which in most instances is at the periphery, while the tygroid substance of the remaining cell has undergone disintegration, appearing in irregular, thick, and broken meshes. The

nuclei are swollen and stain very lightly while the nucleolus assumes a dark stain. The cell prolongations are visible. Many of the cells are gone for the greater part and no trace of the nucleus would be present. The capillaries are filled and in some instances there are thrombi present. These changes are also evident in the sensory nucleus of the fifth and the sensory as well as the dorsal nuclei of the tenth nerves. The nucleus ambiguus shows no change that I would

FIG. 6.—Cross-section of sciatic nerve, showing proliferation of the perineurium, extensive parochymatous degeneration of nerve fibers, and connective-tissue increase; infiltration of leukocytes and Gitter cells. Some thickening of the endoneurium and fatty degeneration of the perineurium. Mallory stain. Zeiss, 8 mm. Oc. 6. × 250.

consider pathological. The cells of the descending and ascending roots of the fifth are very much swollen and show a general chromatolysis with the protoplasm disintegrated into a fine granular mass giving the cell a peculiar dusty appearance. At the periphery there are still evident darkly staining tygroid bodies, and their neuclei when present are eccentric and swollen, staining very lightly with the nucleolus staining somewhat deeper. The cell prolongations of these cells are totally gone and there is no evidence of any peri-

cellular infiltration. The cells of the nuclei of the seventh and twelfth nerves show changes characteristic of the motor nuclei of the bulb at the level of the decussation of the pyramids. In the cells of the other pontine nuclei, the nuclei rubri, and basal ganglia show alterations similar in type to those of third. In the region of the nucleus ruber we find also some perivascular infiltration of mononuclears and endothelials, and also some focal infiltration of small, darkly staining mononuclears and polymorphonuclears as well as some hemorrhages. The glia cell proliferation is very much marked throughout.

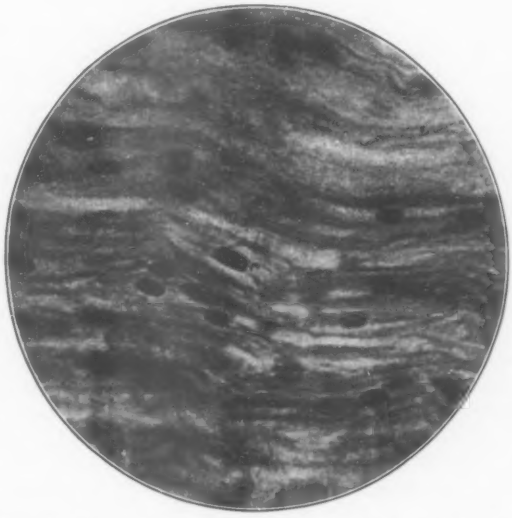


FIG. 7.—Posterior nerve root, lumbar segment showing polyblasts and some Gitter cells. Mallory stain. Zeiss, 8 mm. Oc. 6. × 400.

The spinal nerve roots of all segments stained by the Nissl method show at times a diffuse and at times a focal-cell infiltration into the lymph spaces of the epi-, peri-, and endoneurium. Those of the lumbar segments are most intensely affected. The anterior roots are far more involved than the posterior. This infiltration is not only evident in the distal end of the nerve trunks but also at the entrance of the nerve roots, and which consists of small, round, darkly staining mononuclears, fat granular cells, and polyblasts from which the latter are really formed. At times there is to be seen a hemorrhage into the posterior nerve root, the contiguous white substance of the cord, and into the pia. The thoracic segments are subjected to this change. There is also an infiltration of the perivascular lymph

spaces at the nerve roots which consists of mononuclears and endothelials. The cross-sections of the anterior and posterior nerve roots stained according to methods of Marchi, Mallory, Van Gieson, Bielschowski, and the Nigrosin stain show markedly destructive parenchymatous and interstitial changes. It would seem that the toxic substance has been propagated through the perineural lymph spaces in a comparatively rapid time, producing such extensive and destructive changes. In other places we find a complete breaking down of all the elements of the nerve fiber, a thickening of the endoneurium, and a proliferation of the connective tissue.

The peripheral nerve studied is the sciatic. With the polychrome blue stain there is evident an infiltration of cells, but not as marked in the nerve roots. This infiltration is mainly pronounced in the peri- and endoneurium, and consists of polymorphonuclears, polyblasts, and Gitter cells. Here and there one finds a lymphocyte. The infiltration is most marked in the neighborhood of bloodvessels. There is also a slight proliferation of cellular elements, but their protoplasmic processes are not visible. The connective-tissue and endothelial cells are more proliferated than other cell elements. Especially on cross-section one observes a very marked connective-tissue cell proliferation with their protoplasmic processes extending to some extent between the nerve fibers. The Schwann cells are rather swollen. With the Marchi stain there is to be noted a degeneration of the myelin substance, forming irregular masses scattered throughout the nerve fiber. With the Van Gieson and Nigrosin stains a very extensive nerve fiber destruction is to be seen. The peri- and endoneurium appear markedly thickened, their vessels show a considerable infiltration into their lymph spaces, consisting of large and small round cells. Their endothelial coat is thickened and the endothelium loose. The proliferation of connective-tissue fibers and cells is quite evident. There is also a pronounced infiltration of polyblasts and Koernchenzelln among the fibers. The Schwann nuclei are swollen and stain deeply, and at times fairly occlude the lumen of the fiber. Some fibers show an obliteration of the axis-cylinder, and the myelin substance presenting masses filled with fine, dusty granules assuming a bluish tint with the nigrosin stain. Others, again, show no differentiating characteristics at all, but become confluent into a connective-tissue mass with a marked cell infiltration.

In view of such extensive parenchymatous and interstitial changes in the nerve roots and trunks the question comes up whether we are dealing with end results of a toxin or a bacterial activity, or of both. The cell infiltration would point to a bacterial invasion resulting in a phagocytosis along the lymph spaces of the nerves through which the virus was disseminated. In view of the fact, however, that the infiltration is not marked in all places alike, and in some instances it is rather slight, although the changes in the

fibers are very pronounced, and in view of the fact that the duration of the disease was rather longer than usual, I hold that both the virus and the toxin did play an equal part in bringing about these changes in the peripheral nerves primarily, and these gave rise to the reactionary cell changes in the cord and medulla and pons. The ganglion cell changes, however, which are accompanied by a slight neuronophagocytosis are, in my opinion, the direct result of the virus.

Conclusion. We have here, therefore, a case of ascending paralysis, with attending neuritis, which followed the usual course of extension, later involving the upper extremities and bulbar nerves resulting in respiratory failure. The pathologic findings are definite, involving both the peripheral and central nervous systems. The course of the disease was longer than usually described, extending over six weeks, but otherwise the case was typical in its clinical manifestations.

BIBLIOGRAPHY.

Burghart. Ein Fall von sogenannter Landry'scher Paralyse, Charité-Ann., Berlin, 1897, p. 136.

Korsakow und Serbski. Ein Fall von polyneuritischer Psychose mit Autopsie (im Pueperium), Arch. f. Psychiat., 1891.

Lugaro, E. Pathologische Anatomie, von Flatau, Jacobsohn und Minor, 1904 p. 1138.

Mosny et Moutier, Francois. Paralysie Ascendante Aigue (Syndrome de Landry), Arch. d. méd. expér. et d'anat. path., 1911, p. 285.

Pfeiffer, T. A. F. A Case of Landry's Paralysis, with Special Reference to the Anatomical Changes, Brain, 1912, xxxv, 293.

Wappenschmidt. Ueber Landry'sche Paralyse, Deutsch. Ztschr. f. Nervenh., 1900, xvi, Nos. 3 and 4.

THE VALUE OF SYMPTOMATIC DRUG TREATMENT.

By Joseph L. Miller, M.D.,

CHICAGO.

As compared with a few decades ago, drug therapy occupies a less prominent place in the treatment of disease, and inasmuch as most of our medication is symptomatic in character, it probably means that symptoms are less frequently treated than in former years. Is this to be considered a step in advance, or are we, on account of our interest in scientific medicine, negligent of an important detail in treatment? It is probably true that with the development of specific drug therapy and biological products the physician has become more impatient with and less interested in treatment directed toward giving only temporary relief. Other important reasons, however, must be considered. The profession each year contains more and more men with careful scientific training. This

training may have led them to scrutinize more closely all methods of treatment through carefully controlled observations. The advance of pathological physiology, pharmacology, and experimental therapeutics has furnished them with certain knowledge, and especially a new method of applying it. As a result of all this there has developed, as it appears to the writer, a certain healthy skepticism in regard to drug therapeutics.

Certain points should be considered before undertaking any symptomatic treatment. A few that might be mentioned are: Should this particular symptom be corrected? Does it interfere or assist in bringing about improvement or recovery? Will its modification interfere with making a correct diagnosis or obscure observation upon the progress of the condition? Having determined that a certain symptom should be treated, it is necessary to determine, if possible, the underlying pathological physiology and then the agent to correct it. Not merely the chemical agent but the necessary dosage and frequency with which it should be repeated in order to bring about the desired effect. To attempt to lower blood-pressure, at least under certain conditions, may be poor therapeutics; as, for instance, when due to increased intracranial pressure, when the rise in blood-pressure is an effort to avoid cerebral anemia. It is not improbable that hypertension of renal origin is an effort to increase the efficiency of a pathological kidney. Drug antipyretics, on account of their depressing action, have been largely abandoned in the treatment of prolonged fever. The recent investigation of Rolly and Meltzer and Ludke and others raises the question whether any method of artificially lowering temperature is desirable, as according to their experiments at least a certain degree of fever favors the development of immune bodies. Before undertaking symptomatic treatment it is wise to consider the compensatory resources of the body and not confuse compensatory action with what is commonly regarded as a disease symptom.

In the severe acute infection if we decided the centres in the medulla are not functioning properly can we modify them by certain drugs? We are taught by the pharmacologists that strychnin quickens and deepens the respirations and stimulates the vasomotor centre, causing slowing of the pulse and a rise in blood-pressure. Now if these same results were produced at the bedside upon these centres, rendered abnormal by toxins, we would have in strychnin a valuable symptomatic remedy. Whether under the conditions mentioned, and in the usual doses, strychnin stimulates these centres sufficiently to bring about any appreciable improvement is exceedingly doubtful, as shown by the observations of Cabot, Newburgh, and others. We must therefore conclude that either our conception of the pathological physiology is incorrect, and the recent work of Newburgh indicates that in this particular illustration this may be the case, or our pharmacology is

at fault. Symptomatic treatment, however, when applied to the correction of undesirable symptoms by agents that have been demonstrated to correct this disturbance is strictly scientific, and in this respect is placed at once on the same level as specific therapy.

There is another group of conditions in which symptomatic treatment is not only strictly indicated but in which the agents are at hand to give relief. Morphin when administered to a pneumonia patient with acute pleurisy not only relieves the pain, but deepens the respiration, improves the oxygenation of the blood, promotes sleep, and thus becomes far-reaching in its results. In an acute attack of pulmonary edema, morphin is often of considerable value, in a measure due to its relieving the patient's fears and thus lowering the arterial blood-pressure, and so permit of a restoration of function of the left ventricle. Morphin in acute biliary or renal colic relieves pain, and at the same time relaxes muscular spasm, thus allowing the calculus to escape. Adrenalin, by relieving bronchial spasm, may abort an attack of bronchial asthma. Angina pectoris when due to spasm of the coronary artery may be relieved by the nitrites.

There is another group of conditions in which symptomatic treatment may give only transitory relief, but when combined with other agents may give prolonged relief. This form of symptomatic treatment can only be considered scientific when associated with these additional measures; as, for example, digitalis, although claimed as a functional remedy, is nevertheless, given to relieve symptoms, as, for instance, dyspnea. Alkalies are of value in relieving gastric hyperacidity. The digitalis, however, should be combined with restriction of physical exertion and the alkalies with the proper dietary measures in order to give lasting results.

Outside of the symptoms that can be placed in these groups mentioned or others of the same rational character, there is another group the treatment of which at least today cannot be considered as proved rational therapy. Here might be included the value of salicylates in acute arthritis, of expectorants, of bitter tonics, of arsenic in anemia, and of drugs used to control hemorrhage. It is in this field that the clinical therapeutist can render real service. Here a process of elimination is necessary in order to place therapeutics upon the same high plane as the other branches of medicine.

In addition there is a long list of drugs employed symptomatically proven to be without value, mentioned or recommended still in modern high class text-books. As an example we might name hexamethylenamin, which rapidly acquired a reputation as having bactericidal properties throughout the body and when administered by mouth to appear in the form of formalin in the various excretions and secretions of the body. It is still extensively used

in respiratory and ear infections, in meningitis, arthritis, and cholecystitis; although it has been clearly demonstrated that the hexamethylenamin is only split up and formalin set free in an acid media and of the various secretions, the urine is the only one which is acid.

In order to determine the value of symptomatic treatment it is very essential that the observer be familiar with the course of untreated disease. Individual variations must always be taken into consideration. Many patients with pernicious anemia grow progressively worse, others have prolonged periods of spontaneous improvement, the latter offering a dangerous pitfall for the unwary therapeutist. Perhaps in the teaching of clinical therapeutics it would be wise to instruct the student first in the course of untreated disease; if possible to follow a few cases in the ward, tabulating symptoms, their intensity and duration. He would thus be impressed with the importance of carefully recording symptoms. He would thus be in a better position to determine the effect of therapeutic agents, and so avoid the error of acquiring experience in clinical therapeutics in a haphazard and time-consuming manner. For the purpose of arriving at accurate information too much stress cannot be laid upon the statistical method of which Dr. Osler has always been a strong advocate. While the impression of our therapeutic accomplishments may be more pleasant to consider, it is carefully collected and recorded information that is of lasting benefit to medicine. Our therapeutics can be placed upon the same accurate basis as pathology and symptomatology. Symptomatic treatment is most important not only from the stand-point of the patients, but also for the purpose of clearing up the field of clinical therapeutics, and he who undertakes a careful study of symptomatic therapeutics will be rendering a lasting service to medicine.

THE PROBLEMS OF NEPHRITIS FROM THE CLINICAL STAND-POINT.

By Arthur R. Elliott, M.D.,

PROFESSOR OF MEDICINE, POST-GRADUATE MEDICAL SCHOOL; PHYSICIAN TO ST. LUKE'S HOSPITAL, CHICAGO.

Until a comparatively recent period our knowledge of nephritis was mainly accumulated by the methods of clinical observation and anatomical research. Clinical study has slowly and laboriously amplified in matters of detail the essential facts contained in Bright's original conception of the clinical pathology of kidney disease, but has failed to alter or in any important degree to add to the fundamental principles outlined by the founder of renal

pathology. The study of the morbid anatomy of kidney disease with resulting attempts to form classifications based thereon begun by Frerich in 1851 still continues, although latterly with less enthusiasm for such elaborate classification as characterized pathological research in ultrascientific circles twenty years ago. This decline in the vogue of pathological classification followed inevitably the too great intricacy of many of the classifications and their frequent failure to correlate satisfactorily with clinical manifestations and urinary signs, resulting in division and subdivision beyond the point where the various types can be recognized clinically. With the realization that the methods of pathological study alone offer little prospect of an interpretation of many important aspects of renal pathology, investigation has turned to the study of nephritis in animals produced by experimental technic. Such investigations appear to lend themselves ideally to this purpose, since they include studies in function as well as morphology, thereby overcoming, partially at least, one of the serious shortcomings of purely histological research. These studies in experimental nephritis, actively prosecuted for a period of ten years, while they have added greatly to our knowledge concerning the function of individual parts of the kidney and the way these functions are disturbed in lesions of different kinds, have as yet failed to elucidate important points in pathogenesis. The effect to this point, of the experimental investigation of kidney problems, upon the clinician has been to add to the difficulties of an inherently difficult subject. Enough has been done to indicate that many former beliefs were erroneous; old convictions have been unsettled without the substitution always of definite and reliable information. This inevitably marks the middle stage of any investigation, and need not shake our faith that experimental investigation will finally solve the many important problems concerned.

Coincidently with and largely as an outcome of these activities in research aspects of nephritis the progress of science has introduced new factors into the clinical outlook that afford us valuable aid in the examination of nephritis patients and materially assist us in our attempts to secure a good basis for diagnosis, prognosis, and treatment. Advances in our understanding of chronic infective processes and their relation to systemic disease, the introduction of the blood-pressure gauge into general practice, a more scientific procedure in dietotherapy, and the perfection of tests for kidney function combine to render clinical procedure much more exact and scientific than formerly. It is now no longer enough to state that the patient has acute or chronic nephritis. The diagnosis must be completed with an attempt to elucidate its cause, with an adequate study of the circulation, with an estimation of total renal function, and if we strive to be exact, with a further specification as to whether there is retention of chlorides or nitrogen. Modern

procedures enable each of the above factors to be studied. It is with the bearing on clinical considerations of these newer aspects of the nephritis problem that the present discussion is concerned.

The problem of acute nephritis is essentially different from that of chronic nephritis. In acute nephritis we have to do with acute damage to normally functioning organs which, previously sound, are again more or less quickly restored to normal provided they are not overwhelmed by the destructive agent. In the chronic nephropathies it is the possibilities for the establishment of compensation that constitute the problem. The etiology of acute and subacute nephritis may be said to be invariably either bacteria or their toxins, and of the bacteria concerned, by all means the most important is the streptococcus. This intimate connection between sepsis and nephritis has been frequently mentioned in literature since Bartels first noted it in 1877, but the full extent of the role played by bacteria has hardly had sufficient appreciation. Acute nephritis is usually due to the action of bacterial toxins, the renal reaction being a diffuse inflammatory affair. More rarely nephritis may result from actual lodgement of bacteria in the kidney substance (bacterial thrombi), when cocci may appear in the urine, giving rise in consequence to a disseminated focal type of lesion, of which a good example is the embolic glomerulonephritis of subacute bacterial endocarditis. The existence of acute nephritis (excepting, of course, the rare chemical nephritides) invariably points to a pre-occurring infection. In seventeen cases of acute and subacute nephritis studied by Ophüls,[1] all were found to be suffering from septic processes. The importance of identifying the original source of the sepsis is great, for upon its detection and removal depend, during the earlier stages at least, success in controlling the renal secondary. The tendency of uncomplicated acute nephritis is to recovery, provided infective factors be no longer present and active to work new damage to the kidneys. This is well shown in clinical experience, on the one hand, by the complete disappearance of the nephritis of scarlet fever in those cases that survive, and, on the other hand, by the marked tendency to chronicity that characterizes nephritis associated with tonsillitis, owing to the frequent persistence of focal infection in the tonsil. As illustrating the latter point may be mentioned a recent case where a subacute hemorrhagic nephritis of four months' duration in a child, aged ten years, disappeared within three weeks following radical removal of infected tonsils.

In the matter of chronic nephritis the problem of etiology is much more difficult. The material has been worked over by generations of pathologists, and yet the etiology of most cases is entirely obscure. No doubt in a certain proportion of cases

[1] Arch. Int. Med., 1912, ix, 156.

a history of acute nephritis may be elicited, but the connection between the two is not always clear. There is one difficulty that presents itself from the clinical side in investigating the question of the connection between acute and chronic nephritis, and that is that acute and subacute nephritis may occur without the development of symptoms, other than the urinary signs, during any infection, and failure to analyze the urine may sacrifice the opportunity to discover the original first link in the chain that perhaps leads to a final chronic nephritis. In consequence of this it is difficult, if not impossible, to exclude an antecedent acute nephritis in any given case. Considering the nature of chronic renal disease and what we know of the action of chronic focal or confined infection (sepsis), it would appear likely that certain types of chronic nephritis follow less frequently single acute renal inflammation than that they eventuate from repeated subacute inflammatory reactions consequent upon rise and fall in the activity of chronic septic foci such as exist in infected tonsils sinuses, etc. I have recently observed three distinct attacks of subacute nephritis, with pus in both maxillary antra, in a young man, during the space of one year. Drainage of the antra resulted in prompt disappearance of this renal secondary. Müller expresses the opinion that a chronic nephritis may be the result of an acute lesion with a progressive course marked by acute exacerbations. Our present understanding of infective secondaries would indicate that a progressive exacerbative acute nephritis is the product of a persisting infection or of recurring acute infections. This is the type of chronic kidney met with in association with chronic focal or confined infection (sepsis). Experimenters have found that acute nephritis induced artificially rapidly disappears and that the kidney returns to normal. This is in keeping with the well-known clinical observation that an acute nephritis if its causative agent be no longer operative usually goes on to healing without the development of subacute or chronic lesions. Many cases of chronic nephritis apparently following the acute lesions of scarlet fever have been reported, and both Müller and Löhlein describe a type of chronic nephritis developing several years after acute lesions of scarlet fever and coccus infections, the inflammatory glomerular changes of the primary acute nephritis apparently serving as the starting-point for later fibrotic and indurative lesions. Whether a certain number of these chronic lesions are not spontaneous in origin appears a fair question. The experimental study of nephritis in the main supports the more common conception of the etiology of chronic nephritis in man—that it is a gradually developing lesion due to the long-continued insidious action of some ill-defined toxic substances (Pearce[2]). When we consider what these toxins are, very little

[2] Arch. Int. Med., 1910, v, 133.

clear information is available. Apart from the subacute and chronic inflammatory types of nephritis in which chronic sepsis, including syphilis, can be identified or clearly inferred, we are at present ignorant of the ultimate cause of chronic nephritis aside from the well-known ability of chronic lead intoxication to cause progressive kidney lesions. Recently an increasing importance is being attached to the etiological role of circumscribed and confined infection commonly called focal infection, and it is assumed that it may prove to be an important factor in the production of chronic nephritis. That it may play a first-class role in the causation of subacute and chronic inflammatory nephritis is already fully recognized, but the connection between such a factor and the vascular nephropathies (contracted kidney), while possible, remains for investigation and observation to prove. A certain percentage of cases of this class belong to the type known as secondary contracted kidney. This is the terminal atrophy of acute inflammatory reactions, and as such has a more or less remote connection with acute nephritis, although the original infection or sepsis may have long since ceased to operate as an etiological factor. The tendency of acute nephritis when it becomes chronic is toward either epithelial degeneration or interstitial fibrosis. Epithelial degeneration eventuates in the large white kidney ("parenchymatous nephritis"), whereas the fibrotic organ becomes the so-called secondary contracted kidney. Herringham emphasizes the fact that these are not consequent the one on the other, and he thinks much of the confusion existing arises from regarding them as sequential. Each is individually a terminal development of what was primarily the same acute process. Herringham employs an excellent illustration to define this divergence by citing the development of pulmonary tuberculosis which in one case proceeds by a continuously spreading bronchopneumonia, with softening and cavity formation, while in a second case the tendency is markedly toward fibrosis. In somewhat similar manner typical cases of diffuse nephritis in full development may differ so widely both in clinical symptoms and pathological appearances that they might be two separate diseases. There is, however, no greater difference in these two terminations of acute nephritis than there is in the two forms of phthisis, one a caseating tuberculous bronchopneumonia and the other fibroid phthisis. It has generally been assumed that secondary contracted kidney is uncommon, and the older authorities looked upon it as a great rarity. We are beginning now to understand that it is comparatively frequent, principally owing to the work of Löhlein. He succeeded in collecting quite a number of cases that clinically as well as anatomically were evident examples of this type, and he pointed out that on account of the comparative ease with which he discovered such cases they cannot be as rare as was formerly believed. In Ophüls' series the so-called secondary

contracted kidney was responsible for 11 out of 37 cases of seriously contracted kidney, a percentage that furnishes a startling indication of its frequency.

From the clinical stand-point it is not surprising that these cases are seldom differentiated. There are no absolute and reliable symptomatic criteria that suffice to identify them. In those cases where a clear history of acute nephritis exists, and no doubt intrudes that it was a genuine acute nephritis and not an acute exacerbation of a chronic although perhaps latent lesion, the assumption may be reasonably plain that the secondary contracted kidney exists. Anyone who has looked into the question will recognize that the cases of contracted kidney that give a history of an acute beginning are a small minority. Far the greater number begin insidiously with no severe symptoms. They are either discovered accidentally or an acute exacerbation supervenes which is at first thought to be a primary acute attack until careful inquiry or subsequent observation makes it certain that nephritis has existed for a long time. The secondary contracted kidney in its clinical manifestations closely resembles primary contracted or what is generally known as chronic interstitial nephritis. Such differences as exist are in degree rather than in kind. The clinical picture is perhaps more frequently dominated by a glomerular oliguria, although if a sufficiently large part of the filter apparatus is spared there may be polyuria for the same reason as in primary contracted kidney. As Aschoff[3] points out, the primary factor at work being an inflammatory change affecting the filter apparatus itself (glomerulonephritis), the organ is placed under a more serious handicap as to filtration area than is usually the case in primary contracted kidney. In consequence of this, function is maintained with difficulty, the organs working constantly on the borderline of their maximal capacity. The course of the disease is apt to be characterized by a delicacy of functional adjustment that is easily deranged by the slightest untoward influence, the clinical progression is inveterately downward, with pronounced toxic secondaries (albuminuric retinitis, uremia, high blood-pressure), and almost complete lack of amenability to treatment. There is no primary disease of the glomeruli in primary contracted kidney, the atrophy developing as a result of vascular disturbance from primary sclerosis of the renal arterioles beginning relatively early in life from some unknown cause. What produces the primary disease of the smallest arterioles is still unknown, and we are equally in the dark as to whether the renal mischief precedes, accompanies, or follows a general disease of the vascular channels. The balance of information favors the idea that they are coincident. There is no doubt much justification for the claim made by pathologists that clinically too much emphasis is placed on the kidney element in so widespread

[3] Arch. Int. Med., 1913, xii, 123.

an arterial disease as the primary vascular nephropathy. It is easier to criticise clinical procedure in this matter than to discriminate in practice. The clinician finds himself greatly embarrassed when it comes to appraising the relative value of heart, vascular, and renal changes in these widespread vascular renal degenerations. At least three types of cases are included in this grouping, *i. e.*, arteriosclerotic (senile) renal atrophy, genuine (primary ?) contracted kidney, and secondary contracted kidney. The first of these three has a comparatively unimportant renal aspect which ordinarily is better disregarded, but the kidney most certainly constitutes the important factor in the other two types. We have abundant proof, from nearly a century of pathological literature what difficulty the pathologist has experienced in solving this very problem, and no general agreement even now exists as to how arteries and kidneys stand as to pathological value in the development of contracting kidney. The difficulties of the pathologist are certainly no greater than those of the clinician in this connection. Since no definite symptomatic or urinary differences exist to distinguish one from the other form, discrimination becomes very largely a matter of judgment. Painstaking study of the clinical history and close observation of the progress of the case under treatment ordinarily suffice to separate predominantly renal from arterial cases, and the question of type must be left to the pathologist.

Despite advances in our appreciation of the clinical problems of nephritis, the fact remains that in any given case it is impossible to predict accurately by clinical study alone what course the disease will take in development. To furnish grounds for more exact prognosis and more effective management, various methods have been devised for estimating kidney function in an effort to determine at any point in the progress of a case what amount of renal function remains and is available. If one wishes to gather all possible clinical data he will not rest content with a diagnosis of nephritis, but will proceed to determine the degree to which kidney function has suffered. This the functional test enables one in some measure at least to accomplish. Recent medical literature contains many contributions touching the subject of functional kidney tests, and it is now possible to approach the discussion of this question with considerable painstaking study available.[4]

[4] Rowntree and Geraghty, Jour. Pharmacol. and Exper. Therap., 1910, i, 579, ibid., 1911, ii, 393; Arch. Int. Med., 1912, ix; Vogel, Arch. Int. Med., 1911, vii; Baetjer, Arch. Int. Med., 1913, xi, 593; Foster, Arch. Int. Med., 1913, xii; Folin, Denis, and Seymour, Arch. Int. Med., 1914, xiii, 224; Agnew, Arch. Int. Med., 1914, xiii, 485; Frothingham and Smillie, Arch. Int. Med., 1914, xiv; Ibid., 1915, xv; Toleston and Comfort, Arch. Int. Med., 1914, xiv; Rowntree, AMER. JOUR. MED. SCI., 1914, cxlvii, 352; Pepper and Austin, AMER. JOUR. MED. SCI., 1913, cxlv, 254; Thayer and Snowden, AMER. JOUR. MED. SCI., 1914, cxlviii; Fitz, AMER. JOUR. MED. SCI., 1914, cxlviii; Arnold, Boston Med. and Surg. Jour., 1914, clxx; Stengel, Jour. Amer. Med. Assoc., 1914, lxiii, 1463; Austin and Miller, Jour. Amer. Med. Assoc., 1914, lxiii, 944.

All the tests employed for kidney function depend on the excretion of substances administered in known quantity which are recoverable more or less completely from the urine. Although not the first to utilize this method of investigation, credit belongs largely to Schlayer and his co-workers for bringing forcibly to the attention of the profession the possibilities of this means of research. Schlayer adopted the excretion of water and lactose as indicators of glomerular activity and of sodium chloride and potassium iodide as measures of tubular function. By using these substances as tests, according to a comparatively simple technique, Schlayer claims to be able to distinguish certain types of nephritis, there being a close agreement between the excretion of these substances and the respective types of renal involvement. According to Schlayer, vascular (glomerular) nephritis, whether acute or chronic, is characterized by delayed lactose excretion and by oliguria or polyuria according to the sensitiveness of the renal vessels and by a normal sodium chloride and potassium iodide excretion. Conversely, tubular nephritis is shown by a normal water and lactose excretion, and by delayed sodium chloride and potassium iodide excretion. All grades of mixed functional disturbances were found between these two extremes. In a general way it was claimed that the tests point out the severity of the disease, and as they are all delicate, these tests reveal disease at an early stage. Schlayer went so far as to submit a functional classification of nephritis based on the reaction to these tests. These conclusions are based on the assumption that we can test the individual functions of the kidney and presupposes a much more definite knowledge of the physiology of that organ than we in fact possess. Moreover, it is only in acute fatal cases of nephritis that anything like pure system involvement, glomerular or tubular, exists. So far as practical conclusions are to be drawn, too few observations are at hand to prove that functional findings revealed by tests furnish grounds for an anatomical diagnosis. Many considerations render the study of renal function in detail an extremely complex problem, and as the matter stands, the only available methods for clinical usage are such as furnish information regarding the total function of the kidney, their general excretory power. Tests for estimating the general excretory capacity have consisted mainly of the introduction of various dye substances which are excreted in the urine. General agreement accords first place among these tests to the phenolsulphonephthalein test of Rowntree and Geraghty, introduced in 1910; it was at first used most extensively in surgical cases, especially with reference to the question of operations on the urinary organs. It is equally applicable to medical cases, but the results are considerably more difficult of interpretation, and it is only recently that sufficient observations have accumulated to give it a fixed status in this class of cases. The harmlessness and

simplicity of the test render it an easily available clinical procedure. In its application to nephritis, Rowntree and Geraghty have shown from careful studies that the amount of phthalein excreted varies in rough ratio to the extent of the renal damage. In fatal uremia only traces or perhaps none at all of the dye appear in the urine, while in mild and moderate grades of nephritis the amount recovered from the urine may be normal or nearly so. These authors claim, further, that in cardiorenal disease where the heart is failing and the kidneys are passively engorged a low phthalein output is observed at first, rapidly rising as the heart action improves and venous engorgement subsides. An increase in the phthalein index in such a case may be the earliest indication of restoration of compensation, and represents a favorable immediate prognosis. A low excretory capacity persisting after clinical evidence of cardiac improvement points to a severe nephritis and an unfavorable prognosis. Rowntree claims that the routine use of the test may occasionally bring latent kidney involvement to light, and cites the case of a boy who prior to the functional study was considered the subject of a diabetes insipidus, but who after one phthalein test was recognized as a case of advanced nephritis verging on uremia, a diagnosis substantiated at autopsy two weeks later. The authors of the test emphasize the purely empiric character of the investigation, owing to our lack of sound information as to the physiology of urinary excretion; and while attaching a high degree of prognostic value to the findings when positive, warn against a too general prognostic interpretation, inasmuch as the test yields information only so far as renal efficiency or inefficiency can be estimated, whereas death may occur in chronic nephritis from many other factors, cardiac and cerebral in particular, concerning which the test gives little if any information. This method, in common with other functional tests, must in consequence be considered in connection with general clinical study. The value of total function studies in acute nephritis is much less than in the chronic nephropathies because of the rapidity with which marked changes in functional output occur, ranging within a few days from a low reduction to normal. As a general rule, renal permeability is found markedly reduced in acute nephritis when the case appears clinically grave. This has been found to be the case also when acute exacerbations were associated with chronic nephritis at the time the test was made. In chronic nephritis previous to the employment of function testing, no amount of experience and training has enabled the physician to gain an accurate idea of the degree of the involvement of renal function. Perhaps the majority of cases of contracted kidney are clinically more or less latent, and serious or even fatal developments, among them uremia, may appear suddenly without their proximity being suspected. If function testing is applied as a routine, and repeated periodically, a much

clearer view of the situation is secured. Not only may we be warned of the approach of uremia even when no indication of its proximity is revealed by clinical study, but the rate of progression of the nephritis may be followed.

Coincidently with the investigation of the functional adequacy of the kidneys in nephritis, attention has been directed to the estimation of the incoagulable or non-protein nitrogen of the blood as offering a valuable means for securing information of prognostic value. Strauss was the first to systematically study this phase of the nephritis problem. He found that there was generally an increase in the incoagulable nitrogen of the blood which he regarded as evidence of renal insufficiency. During the last few years there is notable in the literature an ever-increasing insistence on the significance of the non-protein nitrogen of the blood. Studies of this nature are particularly to be desired in the investigation of nephritis, for urine study cannot reveal the stage of accumulation of waste products, an accumulation that may vary from almost normal figures to enormous increase in uremia. The normal figures vary from 20 to 30 mgm. per 100 c.c. of blood, a ratio that may be many times increased in fatal uremia. Although the technic for non-protein nitrogen determination offers no difficulties to the well-equipped laboratory, it is unfortunately not readily available to the practitioner for routine clinical employment. Studies of renal elimination by the phthalein test consequently offer great advantage as to convenience and ease of application. The chief drawback attaching to this method of investigation lies in the interpretation of results, for it is quite conceivable that the rate of elimination of any one foreign substance may have no definite relationship to the efficiency of the kidneys in excreting metabolism products. Cases have been reported (Foster, Baetjer) in which the phthalein test gave practically normal figures, yet uremia resulted shortly after. As the non-protein nitrogen index in the blood is admittedly a more reliable criterion of renal efficiency, it is desirable to correlate the elimination of phthalein with the actual retention of nitrogenous waste in the blood. This has been undertaken by Frothingham, Fitz, Folin, and Denis in experimental uranium nephritis. The results of this investigation demonstrate that in general the tests parallel each other as indications of renal function, varying from normal during the course of the nephritis and returning to normal as the nephritis heals, with this essential difference: that whereas the amount of phthalein excreted shows the renal function at the time of the test, the amount of non-protein nitrogen of the blood measures the accumulating difference between the amounts of waste nitrogen products in the metabolism and the amounts excreted. The time element, the duration of the nephritis, is therefore an important factor in the result. It has been known for long that during the course of any nephritis there are certain periods

when the urinary constituents are normal in amount as compared with the intake, and other intervals when they may be decreased or increased. These functional eccentricities of the kidneys, imperfectly understood, may have a bearing on some of the inconsistencies of the excretory tests. Frothingham and Smillie carried out a series of observations of the non-protein nitrogen and the phthalein test in 77 cases of chronic nephritis. From their charts it appears that the phthalein excretion steadily falls as the amount of non-protein nitrogen of the blood increases, the phthalein practically ceasing to appear in the urine when the non-protein nitrogen reaches 100 mgm. (three or four times normal). In a moderate number of cases a surprisingly low phthalein output was shown for which no cause could be found either from clinical findings or laboratory tests. They consider it fair to state that a considerable individual variation above or below the expected average may occur with the phthalein test for which no explanation can be found. They found the relation between the non-protein nitrogen and the clinical findings to be fairly exact. No non-nephritic cases showed accumulation. All the cases with non-protein nitrogen above 50 mgm. per 100 c.c. of blood gave clinical evidence of severe nephritis. In some of these cases the phthalein excretion was fairly good. On the whole, however, the non-protein nitrogen varied inversely with the excretion of phthalein in the urine. The accumulation of waste nitrogen seemed to be much less influenced by cardiac and other complicating factors than the phthalein excretion. Agnew undertook studies to determine what relation if any exists between phthalein output and non-protein nitrogen in the blood. He concludes that in general cumulative phenomena occur only when the phthalein excretion falls below 40 per cent. for two hours. This is in keeping with the conclusions of Folin, Denis, and Seymour. Tileston and Comfort found that cases of chronic nephritis without symptoms of uremia showed normal or only moderate cumulative signs, the uremic cases, on the contrary, showing a great increase in the non-protein nitrogen of the blood, the excretion of phthalein being roughly proportionate to the degree of retention. Rowntree, Fitz, and Geraghty show that chronic passive congestion of the kidneys gives rise to reduced excretion of phthalein in the urine without marked increase in the incoagulable nitrogen of the blood, and Agnew has been able by this contrast to separate cardiac cases from those having chiefly renal involvement. Austin and Miller report observations of the effect of sweat baths on the non-protein nitrogen of the blood in 11 cases of hypertensive renal disease. They find no evidence that sweating leads to any significant change in the blood waste accumulation. Thayer and Snowden attempt to throw some definite light on the clinical value of the phthalein test in prognosis by comparing the findings of the test with the anatomical

alterations revealed at necropsy in 54 cases of nephritis of different types. In no instance of grave nephritis did they fail to find a material reduction in phthalein excretion. Their study reveals a progressive diminution in the output of the dye which they consider so definite as to give the test a considerable prognostic value. They conclude that there occurs in severe chronic nephritis a uniformly low phthalein excretion which, as a rule, in those instances not interrupted by an acute terminal process, decreases steadily up to the onset of uremia and is nearly or wholly suppressed from a day or two to a month before death. Acute terminal uremic developments which may be unsuspected clinically are common, and here a sudden diminution in the elimination of phthalein may come on in cases where the percentage previously excreted is not so low as to appear alarming. In not a single instance, and indeed not once in all their studies of five years, have these authors met with a good phthalein excretion in a case of severe chronic nephritis. Their observations with the test in 20 cases of chronic passive congestion from cardiac insufficiency conform with the findings of Rowntree and Fitz, and they consider it clear that chronic passive renal congestion alone may result in marked reduction of phthalein excretion which may return to normal as compensation is reëstablished. The foregoing discussion briefly reviewing the main facts brought out by investigation point to the high value of the estimation of the non-protein nitrogen of the blood in the diagnosis of uremia. That it constitutes the most reliable prognostic criterion we possess in chronic nephritis is beyond question. Owing to its greater clinical availability, great interest attaches to the reliability of the excretory test of Rowntree and Geraghty as a means of showing the proximity of uremia. Accumulating clinical observation and the fact that its results in the main parallel the estimation of non-protein nitrogen of the blood encourage the belief that its findings are within certain limitations reliable for prognostic purposes. A certain degree of latitude below expected normal figures should be allowed in carrying out this test, since it appears that only when the excretion of phthalein falls below 40 per cent. do cumulative phenomena develop. In interpreting its findings, it is to be remembered that the test shows the functional power of the kidneys at the time of the observation, and for the dye only, and its indications should not be trusted too implicitly or over too long a period without repetition of the observation. The influence of chronic passive congestion from cardiac causes is to be borne in mind. If excretory values are low and cardiac insufficiency is not present as a factor, we should not disregard the warning simply because clinical indications of uremia are absent, and, on the other hand, if symptoms indicate danger, their significance is not to be neglected merely because phthalein excretion is normal. No absolute prognosis as to duration of life appears possible on

functional findings alone, because we do not yet know how low the phthalein excretion may go and yet be compatible with a renal efficiency sufficing to maintain life, provided the diet and hygiene of the patient are properly adjusted. It is extremely doubtful whether the phthalein test can be employed to any important extent in the diagnosis of nephritis. Routine observations with the method show an output well within the normal limits in the majority of cases classed as nephritis, with good cardiac compensation, except in severe cases, and when in long-standing involvement the actual physiological margin of active secreting tissue has been encroached upon. In so-called cardiorenal disease it is often a most puzzling problem to determine the relative importance of the renal moiety as compared with the cardiac and circulatory. It may happen that the evidence furnished by this method of estimating total renal function will help to elucidate this point. After some experience with the phthalein test covering a period of two years, I am encouraged to believe that it may be used to advantage in the clinical study of nephritis and high blood-pressure states generally. In most instances its value will prove a negative one, but at times and often when least expected a low excretory index will appear. Pending a repetition of the observation, such a case should be handled conservatively, and if the low ratio proves to be a fixed characteristic, and provided cardiac insufficiency be not present to discount the finding, sparing the kidney and brisk elimination must be the principles of treatment. In pending or actual uremia excretory values are minimal and possess the gravest significance. Every case of nephritis should have the test administered at intervals in order to keep track of the functional index, and perhaps thereby mark the progress of the disease. Moderate reductions are probably not of grave prognostic importance unless it can be determined by repeated tests that such is the established state of renal function.

The clinical and experimental research of recent years bears in many important ways on the problems of treatment. Except in rare cases we are still ignorant of the ultimate cause of chronic nephritis, and accordingly a causal therapy is still an ideal for the future to realize. The work of Rosenow, Billings, Eppinger, and others directs attention to chronic infections as an important etiological factor in obscure systemic disease. The fact that chronic septic foci may be latent for years in tonsils, teeth, sinuses, prostate, seminal vesicles, Fallopian tubes, etc., has but lately been fully realized. On the theory of intensity and duration of irritation, a principle well demonstrated in experimental nephritis, the possibility of chronic nephritis arising from low-grade prolonged sepsis must be reckoned with. In the case of an acute nephritis that fails to heal after the original causative infection has apparently disappeared, it becomes appropriate to inquire into the

possibility of a persistent residual infective focus that is operating to render the nephritis chronic, and diligent search should be conducted to discover such a focus and to eradicate it. Since the toxic glomerular nephropathies are most often due to streptococcic toxins, the possibility of such a complication should be thought of in every case of streptococcic infection, especially tonsillitis. The urine should be watched carefully and convalescence attended to with more care than is usually done. As a matter of great clinical interest the recommendation of Billings[5] should be carried out. Every patient presenting evidences of nephritis or cardiovascular disease should be carefully examined with reference to previous infections which might be related to the existing disease and also for the presence of chronic focal infections somewhere in the body. When a focus of infection has been located and seems rationally related to the systemic condition, it should be eradicated if possible. We should not arrest investigation until search has been thorough and complete, for it is possible that two or more separate foci exist, and if we are to secure full prophylaxis all must be obliterated. This successfully attended to the chances of progression of supposed toxic secondaries may be greatly reduced.

The frequency with which chronic nephritis is found to exist in individuals who have been syphilitic for years makes it desirable to investigate this point in all cases where the etiology is obscure. The certain history of a primary lesion will, of course, at once direct suspicion in that direction, and an appeal to the Wassermann reaction may prove the point. Stoll[6] has recently directed attention to the importance of hereditary syphilis in the etiology of renal and arterial disease. The relationship of syphilis to arterial disease is well known, and it has long been familiar that syphilis may cause arterial hypertension. Schottmüller reports a positive Wassermann reaction in over 40 per cent. of his cardiac cases irrespective of the lesion. Congenital syphilis and even congenital syphilis in the parent may have the same effect on the fetus and infant as has acquired syphilis. Clinicians the world over have observed families in which many of the members succumbed to heart and arterial disease. It has been recently suggested that inherited syphilis might be an important factor in such instances, and the observations of Stoll apparently indicate that this is a fact. Cassel found renal changes in ten out of twelve syphilitic infants, and Murphy and Powers state that the renal lesion is, as a rule, a chronic nephritis sometimes latent and sometimes showing active periods. There is need of assigning to syphilis a far more significant influence in the etiology of arterial disease and the vascular nephropathies. Not only should the Wassermann test be carried out as a routine in obscure renal and cardiorenal disease,

[5] Arch. Int. Med., 1912, ix, 4.

[6] Jour. Amer. Med. Assoc., 1914, lxiii.

but a far more painstaking inquiry into the family and personal history should be made than is usually done. Death in middle life from cerebral hemorrhage of the patient's father, frequent miscarriages in the mother's personal history, or deafness in a brother or sister may possess the same etiological import as luetic stigmata or a positive Wassermann in the patient himself. The discovery of syphilis at once prompts resort to antisyphilitic medications. Hopes of improvement to the renal condition by this means are often doomed to disappointment. If the renal disease be not too far advanced a considerable influence over further progression may be gained, although advanced nephritis is more often harmed than helped. To push arsenic, mercury, or the iodides in advanced nephritis is to court disaster.

Before abandoning investigation into the etiology of obscure cases of chronic nephritis in the search for a causal therapy the prevalence and insidious nature of chronic lead intoxication should not be lost sight of. A careful inquiry as to the patient's occupation and environment should be made and the blood examined for basophilitic stippling of the red cells and the urine and feces tested out for lead. The history of exposure is the all-important factor in the diagnosis of plumbism. The significance of occupation and consequent exposure to lead absorption is shown by Hayhurst,[7] who found in varying degree the signs, symptoms, and after-effects of chronic plumbism in a total of 70 out of 100 painters apparently enjoying good health.

After all lines of investigation have proved unproductive, we are in most cases forced to fall back upon the mysterious world of metabolism and to accept such explanations as gout, hyperalimentation, persistent nervous overstrain, or other equally vague idea to account for the vascular renal degeneration. Errors in diet and faulty methods of living, although unsatisfactory as first causes, are nevertheless of quite considerable importance in perpetuating and aggravating existing renal lesions. Under careful management the condition of the average nephritis patient cannot only be greatly ameliorated, but the span of his life can undoubtedly be materially lengthened.

The history of diet therapy in nephritis is dominated by the principle of protein restriction. Modern research during the past twenty years has borne particularly on the mechanism and consequences of retention in nephritis, and the idea of sparing the kidney has been the first rule in diet. In acute nephritis, and during the acute inflammatory exacerbations of chronic nephritis, a large protein intake is undoubtedly unphysiological and exercises an unfavorable influence. During the stormy but relatively short session of acute nephritis the eliminative functions of the kidney

[7] AMER. JOUR. MED. SCI., 1914, cxlvii,

are carried on with difficulty, the renal filter at times refusing even to pass water through it. Attention should consequently be concentrated on the diseased organ, and until convalescence is established, low food intake, even at times to the point of starvation, will best serve the interest of the patient. In such cases for the period necessary the nutritive problem may be submerged in the imperative needs of the choked and irritated kidneys. In chronic nephritis we are compelled to keep the general condition of the patient more in view. Granting the clinical justification of protein conservatism in the diet therapy of chronic nephritis, it is probable, speaking generally, that its severity and duration are much less influenced by manipulation of the protein ration than is commonly supposed. Our efforts in this direction have hitherto been governed by empiricism without scientific means of control, and we consequently have been far too much influenced by routine in the hope of controlling nitrogen excretion, which, after all, can hardly be considered an accurate measure of the gravity of a case. In chronic nephritis, nitrogen excretion is variable beyond explanation, and peculiar kinds of diet do not appear to influence it to any important extent. So far as can be seen at the present time the only reliable criterion available for regulating the protein intake in nephritis is the determination of the amount of waste nitrogen retention by blood analysis. That it is possible to reduce the urea and waste nitrogen of the blood to normal or less is abundantly proved by the feeding experiments of Folin, Denis, and Seymour,[8] and Frothingham and Smillie.[9] Cases with considerable retention require a restriction of protein, and by this means a return to normal figures may be brought about if the azotemia be not too severe. In cases of outspoken uremia no marked reduction of the azotemia results from a protein-free diet. Folin, Denis, and Seymour state that the response to the phthalein function test can be reduced by one-half before abnormal accumulation of non-protein nitrogen takes place in the blood. This estimate is in keeping with Agnew's statement that at 40 per cent. phthalein excretion cumulative phenomena appear in the blood. In clinical practice then it may be assumed that accumulation of waste in the blood begins at about the point where response to renal function testing by phthalein drops to 40 per cent. in two hours. Routine observations with this readily available test may thus enable one to appreciate, with much greater precision than is possible from clinical observation alone, the point (40 per cent. or lower) where positive protein restriction should begin. When the functional index is normal or nearly normal in contracting kidney it is difficult to understand what harm will result to the organs, provided no inflammatory element is present, from a protein allowance based on physiological

[8] Arch. Int. Med., loc. cit. [9] Ibid.

needs. This being the case, we need no longer feel that some trifling miscalculation in the protein ration will jeopardize the welfare of the nephritis patient, nor that it is necessary to draw fine distinctions between various forms of protein. Aided by periodic functional testing to check up the condition of the kidneys, and with our present knowledge of physiological food requirements for good nutrition, the dietotherapy of chronic nephritis may be adapted with reasonable safety, if not, perhaps, with accuracy, and with due realization that in so chronic a disease, general nutrition and kidney conservation should stand on a parity.

Next in importance to the question of nitrogen balance and the protein ration in the diet of nephritis stands the interest that attaches to the ability of the kidneys to excrete chlorides. Since Widal called attention to chloride retention and its relation to edema, a salt-poor diet has been much employed, and while the results are not always as brilliant as Widal predicted, it has nevertheless become a well-established measure in the diet therapy of nephritis. In a general way the chloride excretion parallels nitrogen excretion in acute nephritis, although exceptionally it may fall below nitrogen or even below water. These are cases usually marked by dropsy. In chronic nephritis, chlorides do not run parallel to the urinary nitrogen. Although certain cases occur in which the chloride output is fully equal to the normal, more or less deviation is the rule. Subacute exacerbations of chronic nephritis determine definite periods of chloride retention, marked frequently by more or less edema, subsequent compensatory hypersecretion occurring as the dropsy subsides. In exceptional cases an inherent inability to excrete chloride may exist. A resumption of chloride function may frequently be brought about in such cases by withdrawal of salt from the diet. Observations on experimentally induced nephritis in animals seem to indicate that chloride retention depends on injury to the tubular structures of the kidney, whereas vascular (glomerular) changes produce no such effect. This fact may give us some insight into the underlying anatomical changes in certain cases marked by persistent chloride retention, although it is doubtful if such clear deduction should be drawn owing to the mixed type of nephritis encountered clinically. That chloride excretion is generally deficient in edema and that increase in chloride excretion coincides with disappearance of edema are clinical facts frequently observed. There is doubt, however, that the vogue of salt restriction, extensively and empirically enforced in all forms of nephritis, is justified by the established facts. Obvious contradiction to this practice is apparent in certain experiences with the so-called Fischer treatment of nephritis. The "fear of salt" apparent in the diet therapy of nephritis, subjects many patients to useless and burdensome hardship without care being taken to establish

the fact that the kidneys actually retain chloride. Vogel[10] discusses this question and advocates a more rational and scientific procedure. Whatever may be thought of the salt-poor diet as a routine in nephritis, the indications to be secured from a study of the manner in which the kidneys deal with known amounts of sodium chloride and water are sufficiently valuable to render it advisable to make such determinations in beginning the treatment of at least severe cases of the disease. This is the more necessary, since in chronic nephritis with salt retention a long course of salt restriction is usually necessary to restore function. The technique of chloride tolerance determination is simple. For clinical purposes it is sufficient to conduct for a preliminary period of several days' observations on the amount of urine excreted, allowing the patient to follow his own inclinations as to the amount of fluid drunk, although this should be measured to compare intake with outgo. During this preliminary period the patient is on a mixed but tabulated diet, the chloride value of which should be approximately known. Each day a chloride determination of the twenty-four-hour urine should be made. As soon as it is found to be reasonably stabile, the water intake is doubled for two or three days, and the response in increased diuresis and the effect on body weight noted to determine water retention. Subsequently, the diet remaining stationary, 10 gm. of salt are added to the diet. This excess of salt should normally be excreted in from twenty-four to forty-eight hours, either by increase of salt concentration in the urine or by diuresis. The time of its excretion should be watched by determination in twenty-four-hour urines, and the effect on specific gravity, amount of urine, and body weight noted. This may be repeated at intervals of two or three days for control determinations. In this way the promptness and completeness of chloride excretion may be gauged and a proper basis secured for diet procedure. In cases appropriate for salt restriction it usually suffices to establish a "salt-poor" rather than a "salt-free" diet, an allowance of from 2 to 4 gm. per day being sufficient to produce the result desired without imposing any particular hardship on the patient. As stated above, a long course of salt restriction is needed to restore the excretory power of the kidneys, and the resumption of chloride feeding should be very gradual even after chloride equilibrium is established and edema has disappeared.

The practice of water restriction has been carried to excess in nephritis. Rarely can any advantage be gained by this procedure, except in certain cases of acute nephritis and in contracted kidney with cardiac dropsy. Nitrogen excretion is not influenced to any extent by the amount of ingested water, and in chronic nephritis with uremia fluid control has proved futile. In the early stage of

[10] Arch. Int. Med., 1911, xii.

certain severe cases of acute nephritis with oliguria the amount of fluid should be reduced to the smallest possible quantity. In such cases, to use an expression of Herringham, "the kidney is struck dumb," and for a period is unable to excrete even water; with recovery of function as the severity of the inflammation subsides, water may be progressively increased. The therapeutic problem in chronic nephritis is largely a cardiac one, the fate of the patient hanging almost solely on the maintenance of cardiac strength and an adequate blood-pressure; so that the justification for fluid restriction rests here upon the same basis as in primary heart lesions, *i. e.*, lessening of heart work. Regulation of fluid intake therefore becomes important as a prophylactic measure whenever the heart is to be spared, and also in all cases when edema makes its appearance whether the dropsy be cardiac or renal in origin. Regarding the influence on the height of the blood-pressure of free and restricted fluid intake, clinical observations indicate that it is practically without influence either way. So long as the heart is competent, unrestricted water drinking causes no material increase in blood-pressure, nor does limitation of fluids reduce blood-pressure values. Fluid restriction is called for in cases showing much dyspnea, arrhythmia, and other premonitions of cardiac breakdown. Even after heart failure has begun and edema is present we see good results follow this practice.

According to Strauss, the high blood-pressure of nephritis is usually, or at least frequently, accompanied by an excessive accumulation of nitrogenous waste products in the blood. This is in keeping with the prevalent clinical belief that the high pressures frequently observed in nephritis, and especially the "hypertensive crises," punctuating the course of many cases, are uremic in origin. One of the objects of the investigations undertaken by Folin, Denis, and Seymour already referred to was to determine whether there is any correspondence between the height of the blood-pressure and the accumulation of nitrogenous waste products in the blood. Their observations indicate that high blood-pressure is not necessarily accompanied by excessive retention of waste nitrogen, and they do not consider that high blood-pressure necessarily indicates the desirability of introducing low protein diet in nephritis. They state, moreover, that the wide fluctuations of blood-pressure, often amounting to 40 mm. or more, do not appear to be associated with any accumulative excess or marked variability in phthalein excretion. The observations of Frothingham and Smillie appear to bear out these conclusions, indicating that so far as uremia is concerned the height of the blood-pressure and the degree of pulse-pressure possess no clear prognostic value in nephritis. It is doubtful, however, whether these laboratory investigations are sufficiently numerous or conclusive to form a basis for the abandonment of the long-established clinical impression

that the higher the blood-pressure the more imminent the danger from uremia. Of Janeway's series of 212 cases of high blood-pressure 46 died of uremia.[11] This group along with those dying of cerebral accidents showed the highest average for blood-pressure of any mode of death. Janeway's tables would indicate that, other things being equal, a systolic pressure of over 200 mm. constitutes at least a presumption in favor of termination by uremia or apoplexy.

Although it is true that many patients with a high blood-pressure in nephritis live for an astonishing length of time, the influence of this factor as a source of cardiac and arterial overstrain prejudices the course and finally determines the end of a large percentage of these cases. One of the aspects of chronic renal disease that has been considerably elucidated by experimentation is the pathogenesis of high blood-pressure. By performing successive reductions of kidney substance in dogs, Janeway has been able to demonstrate, after the lapse of several weeks following the completion of the operations, a material elevation of blood-pressure and polyuria, thus apparently establishing a relationship between blood-pressure and the amount of functioning kidney tissue. Thus the fact long recognized clinically that high blood-pressure, cardiac hypertrophy, and polyuria are rendered necessary in chronic nephritis to compensate for destruction of renal secreting tissue receives some support in experimental proof. The sound tissue that remains as the kidney shrinks, works on the borderline of maximal capacity, so long and only so long as its blood supply is maintained at a proper speed and a sufficient pressure. Under this mechanism the only way compensation appears possible is by further heart work at elevated pressure. This accounts for the relatively limited power of accommodation in the advanced stages of polyuric vascular nephritis and the absolute importance of the cardiovascular adjustment in maintaining renal function. From this view-point, if it be the proper one, it appears obvious that high blood-pressure and cardiac hypertrophy constitute a necessary evil that must be put up with, and if, as a consequence, death results from cerebral hemorrhage or heart failure, that is but an alternative to death from progressive uremia which would surely supervene without these cardiovascular secondaries. A good clinical illustration of their importance is furnished by the comparative well-being and symptom-freedom of patients during the stage of cardiac compensation contrasted with their miserable second state supervening with cardiac failure and secondary falling blood-pressure. In large measure, contracted kidney cases are for therapeutic purposes, cardiac cases, to be managed at one time as one would valvular disease during compensation and at another time as valvular disease with failing compensation. The degree of hyper-

[11] Arch. Int. Med., 1913, xii.

tension in patients under forty is most often in direct ratio to the element of uremia, and consequently we should view with concern a sustained high blood-pressure in the young and direct our treatment rather to the kidneys than to the heart. Here the phthalein test may give one important guidance. In older individuals many factors not present in youth enter into consideration, and this is the truer the farther we leave middle life; consequently we need not attach so much significance to high blood-pressure in the old. Cardiovascular degeneration in later life is not so directly proportional to the degree of pressure, other important factors such as arteriosclerosis entering into consideration.

It is possible for a patient with high and even very high blood-pressure to live for years without heart failure or apoplexy. Excessive blood-pressure values do not necessarily imply impending or early disaster. The state of the heart muscle and of the cerebral vessels is hard to gauge, and that is the deciding factor in prognosis and not the blood-pressure range *per se*.

The treatment of high blood-pressure is primarily hygienic. During the period of sustained compensation the entire personal hygiene, including diet, should be so regulated as to avoid all overstrain to heart and kidneys. The greatest emphasis is to be placed on this principle of treatment and no pains spared to enforce obedience in detail. Rarely is it advisable to lower the blood-pressure by direct therapeutic attack. This follows inevitably as a principle of conduct if we grant that high blood-pressure is a compensatory phenomenon. In chronic nephritis only discomfort, if indeed nothing worse, will accrue to the patient from the use of vasodilators. Nitrites should be reserved for emergency use to combat angina, stenocardia, cardiac asthma, severe high-tension headaches, and other pressure manifestations that may supervene in chronic nephritis. If dropsy, either renal or cardiac, exists, nitrites should not be given, as under these circumstances they do only harm. The appearance of dropsy in chronic vascular nephritis almost invariably signifies the advent of cardiac failure. Sooner or later in the course of every case that survives long enough, cardiac edema develops. Because the case is primarily a renal one it does not follow that the dropsy is of renal origin. It is usually cardiac, has the characteristics of cardiac edema, and can not be successfully treated by sweats and diuretics, but requires cardiac supporting measures. Digitalis in the end becomes the staff upon which the chronic nephritis invalid must lean. The reason for this is that after we have enforced the maximum of hygienic and dietetic control we can do no more for cardiorenal hypertension, but must wait until the heart begins to fail, and then we may prolong life for months or even years by the judicious use of digitalis and its congeners. The fact that the blood-pressure is high need not deter us from giving digitalis, since it acts just as well or even better with a high blood-pressure than it does with a falling pressure.

CHRONIC INTERSTITIAL NEPHRITIS AND ARTERIOSCLEROSIS.

By Oskar Klotz, M.D., C.M.,
PITTSBURGH, PA.

(From the Pathological Laboratories, University of Pittsburgh.)

No agreement has as yet been reached as to the nature of and the progressive changes leading up to the granular kidney. Almost all the factors having to do with the carrying out of the normal kidney function, as well as the known factors giving rise to processes of fibrosis in other organs, have been mentioned as the inciting cause of renal sclerosis. Particular weight has been placed upon certain of these factors, because of their presence during one stage of the disease; but the opportunity of weighing their importance as an active cause for the contracted kidney has not been sufficiently good to direct a knowing finger at them. No one has yet been able to describe in a single instance the sequence of events from the beginning to the fully developed chronic interstitial nephritis. Thus, opportunity has remained open for wide speculation on the interpretation of the pathological processes involved.

Some attempt has been made to link up the clinical and urinary findings with the successive changes that are taking place in the tissues of the kidney. These, however, have added little to our understanding of the process. True it is, that with the fully developed disease, certain manifestations make their appearance, and we believe that some light has been thrown upon the correlation of the urinary character with the altered functional capacity due to renal sclerosis. But as for saying that the clinical manifestations bear any relation to the structural change of the kidney prior to the stage of granular contraction or, better, that we can forecast the outcome or even suggest the past processes in the kidney by clinical analyses we have no definite evidence.

Thus the problem has been left in the realms of conjecture and in the absence of incontestable proof by experiment, our knowledge concerning the development of the granular kidney has not materially advanced since the days of Gull and Sutton. In the face of this we do not wish to minimize the value of the many observations which have given us a clearer understanding of some of the finer reactions in the kidney substance; but it would appear that the minutiæ of some of these observations have led us astray from the broad aspects of the problem. That Jores should find a splitting of the internal elastic lamina of the renal arterioles, and from this finding discuss the importance of those still indefinite factors inducing arteriosclerosis as of prime importance for kidney disease, is, it seems to me, quite aside from the main issue.

For the main part, as was brought before the Association of American Physicians last year, studies upon the pathological nature of chronic interstitial nephritis have been made upon the advanced form of the disease. The criterion for the recognition of the important type of the disease is still based upon the description of the kidney as given by Richard Bright. If we adhere closely to these described characters, we will find there is a general similarity grouping them into one class. Gradually, however, our attention has been drawn to the fact that there are other forms of renal sclerosis, differing to a greater or less degree from the type here under discussion and readily recognized by careful observation and supplemented by the microscope. Thus we have kidney fibroses associated with hydronephrosis, ascending infection of ureter and bladder, hematogenous infection (pyogenic), infarcts, thromboses, amyloid disease, syphilis and other infective granulomata, and arteriosclerosis. But when we are speaking of the small, contracted or granular kidney we have in mind a diseased condition of the kidney which is different from each of these. It is different not only in the structural changes induced, but it is different also in its progress and in the distant systemic responses. The small, granular kidney is recognized by its small size, the thickening of its capsule with adherence to the underlying cortex. The kidney substance when stripped of its capsule is distinctly granular, each granule being surrounded by a depression from which fibrous tissue radiates parallel with the ascending vessels. The kidney substance may appear red, but, on the other hand, may be quite pale with not a few of its granules as yellow as the adrenal cortex. The cortex is most markedly altered, and is commonly only half the thickness of the normal structure. Within it are found many fine wedge-like sclerotic areas which occupy the positions between the granules observed on the surface. Alternating with these areas of fibrosis a fairly normal kidney tissue is observed. Along the patch of these radiating fibroses the tubules and Malpighian corpuscles become involved. The medulla is less altered, although a hyaline fibrosis not infrequently surrounds the excretory tubules. As in other regions subject to progressive fibrosis a considerable adipose tissue develops in the surrounding structures, particularly about the pelvis.

At the present time, opinion as to the development of this form of the interstitial nephritis has been divided mainly between two schools: the one considers it the outcome of a low grade but progressive inflammation, while the other believes it the result of a primary circulatory disturbance with a secondary atrophy and replacement fibrosis. Unfortunately the issue has been somewhat confused by the further introduction of the terms primary and secondary interstitial nephritis. Each group claims that their explanation is adequate for the so-called genuine contracted kidney. We would do well to drop such irrelevant terms and leave

the application of a new nomenclature to him who clearly indicates the pathological sequence of events concerned in chronic interstitial nephritis.

Gull and Sutton considered the relationship of the arteries to the diseases of the kidneys as a peculiarly intimate one in which the arterial processes preceded and determined the interstitial nephritis. No agreement was reached by subsequent workers of the actual nature of the arterial disease, some viewing it as an endarteritis (Thoma), others as an hypertrophy (Johnson, Ewald, Friedmann), while the subsequent work by Prym and Jores drew attention to the arterial lesion as a true arteriosclerosis. Jores, furthermore, contended that the associated arterial changes in other organs, as was described by many, was also an arteriosclerotic process. The differentiation of this process rested upon the finding of deep arterial degenerations associated with a splitting of the internal elastic layer. As Jores, however, observed, arteriosclerosis may occur in the arteries of other organs in the absence of sclerosis of the renal vessels.

While the above authors were contending the dependence of chronic nephritis upon disease of the bloodvessels, Ziegler maintained the differentiation of types of chronic nephritis into groups associated or unassociated with arteriosclerosis. Those kidney lesions resulting from arteriosclerosis he believed to be individual and of a purely degenerative character, and designated them the arteriosclerotic kidney.

Both Jores and his pupils repeatedly remarked that chronic interstitial nephritis is a disease most frequently encountered in advanced life, a period when arteriosclerosis is also most prevalent. Nevertheless, they remark upon the finding of occasional cases in which they have been able to demonstrate advanced renal sclerosis unaccompanied by arteriosclerosis within the kidney. This agrees with the finding of Orth, who believes that in chronic interstitial nephritis the vascular changes are not essential because their variety does not correspond with the extent of the lesions. Roth described a number of cases in which renal sclerosis was advanced, but in which the arteries did not show the type of sclerosis defined by Jores as arteriosclerosis. He did, however, find that the arteries were affected by a connective-tissue thickening of the intima with splitting of the elastic lamina. As, however, processes of degeneration were wanting, he refused to call it arteriosclerosis. He suggests that these vessels might subsequently show arteriosclerotic change. From his observations we can only conclude that the kidney lesions have advanced with greater rapidity than those in the intima of the renal vessels, and his cases illustrate the point we wish to make that the narrowly defined form of arteriosclerosis as given Jores is not an essential factor in bringing out subsequent interstitial nephritis.

Roth described 3 cases of chronic interstitial nephritis without arteriosclerosis. In the kidneys, however, endarteritis was present in the small arteries. The cases were of relatively young individuals, and all of them had definite chronic or recurrent heart and arterial diseases. Yet with it all neither Jores nor his pupil sees any direct relationship insofar as a common causative factor is concerned in the simultaneous and progressive lesions in these three organs. These authors lay much stress on the finding of a single sclerosed arteriole or the mildest beginning of intimal degeneration as indicative of the influence of arteriosclerosis upon the kidney. No recognition is given to the fact expressed in their own cases that the fibrosis of the kidney was markedly advanced, and in the late stages of contraction, while the arteriosclerosis was only beginning. We can in no way follow the conclusion of this author as illustrated by his own cases that the chronic interstitial nephritis was the result of the early endarteritis demonstrated.

In the admirable work of Councilman (1897) the part played by the inflammatory process in bringing about the interstitial lesions of the cortex of the kidney was well demonstrated. In part, the cases studied included some of scarlet fever, diphtheria, pneumonia, and other infections, and the lesions described were of the nature of diffuse non-suppurative interstitial nephritis or types of glomerulonephritis. Of the latter, two forms were distinguished: a non-suppurative exudative form and a proliferative type. No clear distinction can be made between the etiological factors present in these two types, and it would seem that both may arise from the same causative factor. At the time of carrying out his work, bacteriological methods were not available to make a distinction between the various forms of streptococci, and we find the author speaking of the organisms isolated from cases of heart disease as pneumococci. I believe we will be correct in interpreting these results as indicating the presence of the Streptococcus viridans group. These organisms were found in cases of glomerulonephritis in large percentage, but the author's descriptions of the lesions indicate a transition between the glomerulonephritis and the diffuse, interstitial type. The work of Wagner bears out these findings, particularly in indicating the importance of the inflammatory process of scarlet fever and other infections in bringing about permanent interstitial change.

The work of Councilman is among the few in which a study of the progressive lesions of the kidney was accompanied by bacteriological examination. Of this he says: "Various forms of disease of other organs, particularly of the heart, are often associated with them, and bacteriological investigation has frequently shown in many cases the presence of certain organisms in the kidneys. In most cases the bacteria are found in some other lesion and in the blood, and their presence in the kidneys is but a part of a general

septicemia. Moreover, the same conditions in the kidneys may be found associated with various organisms, and the same organisms may be associated with widely different anatomical lesions." A very fertile field awaits the routine study of the bacteriology of the kidneys in conjunction with the histological examination of all types of infection. The work which has been performed up to the present time is very suggestive of indicating the actual presence of bacteria rather than their toxins in the interstitial response of the kidney.

Undoubtedly what appears as complete disagreement in the personal observations on chronic nephritis lies mainly in the methods and material studied. Although the anatomical classification of kidney disease has not found favor with either the clinician or the pathologist, yet in the absence of a better substitute we all revert to this method. Müller attempted an etiological classification which as yet is hardly practical, and Herrick, while finding the old anatomical grouping unsatisfactory, offers nothing to replace it.

The types of nephritis which today attract our attention as the forerunners of the contracted kidney are the acute glomerulonephritis and the acute non-suppurative interstitial nephritis. Without desiring to describe the various types of glomerulonephritis, as well as the variety of interesting lesions that may be observed in the Malpighian body and Bowman's capsule, there is ample evidence that, in the human, these glomerulonephritides are infective lesions (Councilman, Gaskell, Baehr). The important feature lies in the fact that the glomeruli become the centres of inflammatory response in which a non-suppurative exudate and endothelial proliferation of the capillaries and a proliferative response of the inner lining of the capsule is commonly observed. The occlusion of the capillaries of the glomerulus by cellular proliferation or by thrombosis is only an added complication, and the subsequent degeneration that occurs in the tubules of the kidney is also to be viewed as a secondary disturbance depending upon vascular change rather than an injury produced by the primary factor.

A study of these cases of glomerulonephritis soon convinces one of the varying picture, even during the acute stage. In some thromboses of the glomeruli are common, in others rare, or the lymphocytic infiltration of the glomerulus is great and confined to this structure; others again, show the inflammatory reaction diffuse, surrounding Bowman's capsule, infiltrating the stroma between the tubules and following the course of the interlobular arteries and vessels of the intermediate zone. Many such cases have been described, by Councilman, Ziegler, and others. In fact, the picture presented by those kidneys in which the inflammation is more diffuse simulates more closely the type of acute interstitial non-suppurative nephritis. This latter type, which was originally discussed as a disease of the kidneys found after scarlet fever,

measles, and sometimes smallpox, is now being incorporated with the glomerulonephritis, mainly because a certain amount of glomerular disturbance is always present. Fahr finds the streptococcus and pneumococcus most frequently associated with acute interstitial nephritis, and finds also that the same organisms are the chief cause of glomerulonephritis.

In short, although there are variations of glomerular lesions, and we encounter forms of inflammation of the kidney stroma, there does not appear to be any difference in the causative agent, most frequently the Streptococcus viridans. We must, however, point out that the bacterial infection reaches the kidney under different circumstances, and in a somewhat different form, in the various systemic diseases in which it is met. It is the bacterial clusters or small infective thrombotic masses which are liberated in heart disease that give rise to a type of glomerular infarction. In this way particular structures in the kidney are more intensely involved than others. So, too, in cases of bacteriemia, by organisms of low virulence, the kidney, as well as other organs, becomes a local focus of infection and this is particularly true in the bacteriemia of acute rheumatic fever in which the heart and bloodvessels are also affected. In these infections the heart may be involved in a variety of ways, and when the endocarditis becomes well-marked the kidney may be subject to embolic processes in its glomeruli, so that both the acute interstitial and the glomerulonephritis are simultaneously prominent. Hence it is obvious that to state that a definite type of kidney lesion is constantly to be found as a disease associated with infection of other organs is only voicing a rule with prominent exceptions.

The frequency with which acute interstitial and glomerulonephritis are present with infective heart disease is known to all who have observed these cases at autopsy and studied the tissues. It is, furthermore, easy to demonstrate the fate of the early inflammatory process. Fibroses of the glomeruli, of Bowman's capsules, and of the intertubular stroma may be demonstrated in all stages of formation, and recurrent attacks of these infective processes give rise to combinations of inflammatory responses in the kidney tissues. The question immediately arises whether the localization of these inflammatory processes gives us definite types whereby their future scars may be recognized. In answer to this the best reference is made to a few experimental results. In these it has been shown that inflammatory reactions in the kidney due to bacterial agents are prone to follow and surround the course of the bloodvessels particularly the interlobular vessels, and the ascending cortical branches as well as the afferent arteries of the glomeruli. Associated with these inflammatory responses there are not infrequently glomerular reactions, infiltrative, proliferative, or thrombotic. The progress of these lesions is similar to that in the human kidney

and the end-result is a process of fibrosis radiating in its character with shrinking and granulation of the cortex and contraction of the entire kidney. Such lesions were reproduced in animals by the use of organisms (various members of the Streptococcus viridans group) isolated from infective heart disease, and the responses in the kidney were found to be accompanied by a myocarditis, at times an endocarditis, and in a few cases pericarditis. In only a few instances were systemic intimal arterial lesions obtained, although the perivascular response was always noted. Here, then, we have evidence of the development of the various stages of the contracted kidney in the presence of chronic infection and in the absence of primary arterial lesions.

These findings are in accord with the observations on human material and explain the occurrence of the contracted kidney in the first half of life as well as its greater frequency in the later years. Like all chronic diseases, the frequency of chronic interstitial nephritis is greatest in the late decades, and it is also a rather depressing outlook when we find that the incidence of these chronic diseases shall increase with the saving of more lives in childhood from death from scarlet fever, acute rheumatic fever, chorea, and other Streptococcus viridans infection. We must also equally appreciate that the heart and arteries suffer, sometimes much, at other times less, by invasion of these bacteria. In the arteries an endarteritis, a mesarteritis, and a periarteritis have all been repeatedly demonstrated in these infections during the early years of life. Of the heart lesions, we need make no other comment than reference to Aschoff's studies upon focal myocarditis, and of the frequent presence of endocarditis in the human and in experimental infections.

What, then, is the relation of renal arteriosclerosis to chronic interstitial nephritis? Before one can answer this we must have a clear understanding of the nature and genesis of arteriosclerosis. It is not enough to boldly speak of general arteriosclerosis as of common type and constant origin. Nor is this true within the kidney itself. There are arterial lesions within the kidney whose origin is widely different and which vary in their character.

Ziegler has long ago demonstrated the peculiar renal fibrosis resulting from peripheral arteriosclerosis. In old age, where it is not uncommon to have various arterial tracts severely involved in sclerosis and in which the lumina of the vessels are distinctly impeded, atrophic changes result in the area supplied. It is obvious that the amount of sclerosis varies greatly and is bound to pick out limited areas. The kidney tissues which suffer from the circulatory disturbances undergo atrophy, and even complete loss, without, however, necessarily showing evidence of intracellular degeneration (fat), as is otherwise so commonly encountered. The kidney shows areas of sharp depressions scattered irregularly

over its surface so that its structure and shape are distorted. The individual depressions simulate those of infarct, but microscopically may at times be distinguished from these in that the involved areas contain some of the parenchymatous structures not completely destroyed. Furthermore, the kidney capsule is rarely adherent and the cortical surface between the areas of depression is relatively smooth.

Such depressions are the result of the obliteration of fairly large vessels within the kidney. At times, it may be, smaller vessels involving more restricted portions of the kidney are affected. This, then, leads to a local fibrosis of the glomeruli supplied by this circulation. Under these conditions the process, both in the glomeruli and tubules, is one of slow and progressive degeneration, with a secondary replacement fibrosis. It is unusual to observe under these conditions any evidence of an inflammatory reaction.

Compared with the granular contracted kidney, these changes in the arteriosclerotic kidney are quite different. It is inconceivable that a process of arteriosclerosis could so uniformly affect so many arterioles of a constant caliber to give the character found in the uniformly granular kidney. A comparable picture is to be observed in no part of the body, and we are well aware how uncertain is the distribution of arteriosclerosis. As the fibrosis following upon processes of degeneration in the atrophies of vascular scleroses is without inflammatory response, one misses entirely the presence of a granulation tissue and subsequent adhesions. The absence of these is noted in the freedom of the kidney capsule and in the lack of synechiæ about the glomerulus. Frequently, too, Bowman's capsule shows no thickening. Ziegler truly calls this the senile kidney.

It is, however, not common to meet with a clear-cut and uncomplicated case. The vascular scleroses of the kidney are most commonly the result of the same influence which has produced a primary inflammatory lesion in the kidney stroma. Hence, the development of scar tissue in the renal structures goes hand in hand with renal arteriosclerosis. Here, however, in the early stage, as well as during the years of progressive involvement, the kidney tissue and arteries show the presence of inflammation. These inflammatory deposits are easily recognized, and obviously vary in amount at the different stages. Jores has seen them in his interstitial nephritis, but has taken the view that no relation between the arterial disease and the inflammation can be determined. Like the results of the Streptococcus viridans infection upon the heart, giving rise to inflammatory processes differently disposed, so, too, this same infection, which is so frequently at the bottom of the fibrosis of the contracted kidney, brings about inflammatory reactions of varying intensity in different portions of its structure. The arteries appear to form the centre of distribution for these

reactions, and much of the response is spent in the tissue surrounding the small vessels coursing through the cortex. To a certain extent, however, intimal reactions are also found. The latter, however, arise somewhat later in the course of the kidney disease, so that examples are not difficult to demonstrate in which intimal sclerosis is wanting while a non-suppurative inflammation is active about the vessel. Later, however, the picture is reversed and the intimal sclerosis attracts our eye. This is now the stage when appearances suggest that a close relation of cause and effect exists between the intimal arteriosclerosis and the renal fibrosis.

The intimal disease of the arteries most commonly met with in the late stages of chronic interstitial nephritis consists of a chronic endarteritis with deep, fatty change. The presence of a true hyperplasia of the musculo-elastic layer with secondary degeneration of the inner muscle bundle has never been met with by us, nor have its advocates ever clearly demonstrated its presence. The finding of splitting of the internal elastic lamina is now found to have no specific bearing on the problem of arteriosclerosis. McMeans (of our laboratory) has shown that such splitting is the common occurrence during inflammatory reactions of the intima.

Granted, therefore, that the early reactions which lead to the granular contracted kidney, simultaneously involve portions of the kidney parenchyma and its arteries, it is often extremely difficult to distinguish in the late stages of the disease exactly how much of the scar tissue has resulted through inflammation or as replacement fibrosis following arteriosclerotic atrophy. We should, however, continue to distinguish clearly the arteriosclerotic kidney of Ziegler from the granular interstitial nephritis, the former giving rise to true atrophic processes in the parenchyma with replacement fibrosis, the latter having an inflammatory basis for the development of connective tissue variously distributed about the important structures of the organ.

CERTAIN SYPHILITIC AFFECTIONS OF THE HEART AND AORTA.[1]

By J. M. Anders, M.D., LL.D.,
PROFESSOR OF MEDICINE AND CLINICAL MEDICINE IN THE MEDICO-CHIRURGICAL COLLEGE, PHILADELPHIA; OFFICIER DE L'INSTRUCTION PUBLIQUE.

A variety of morbid states of the heart and bloodvessels, all serious in nature, may develop during an attack of unquestioned syphilis. While the writer would not go so far as to say, with

[1] Read at a stated meeting of the College of Physicians of Philadelphia, June 2, 1915.

some recent investigators, that syphilis is the principal factor in the production of heart disease, it can at least be safely assumed that rheumatism and syphilis head the list as causes of organic injury to this organ. The advent of the Wassermann reaction has shown, in a convincing manner, that the role of syphilis as an etiological factor in diseases of the cardiovascular system had previously been underestimated. It is frequently the earliest clue to lues, especially in females, who, in many cases at least, know nothing of syphilitic infection, while in other instances a Wassermann reaction will, as has been well said, "unlock the tongue."

The cardiac lesions caused by the Spirocheta pallida are usually considered as belonging to the tertian stage of syphilis, but recent investigators have shown that they may develop soon after primary infection. Grassman[2] and later Brooks[3] and others have expressed the opinion that damage of a serious character may appear as early as the forepart of the second stage. The fact should not be lost sight of that both aortic and cardiac syphilis may be the result of hereditary lues. It is definitely known that the Spirocheta pallida has a selective action for the heart. As stated elsewhere, "of all the viscera the heart is among the earliest to become involved in this disease." The importance of recognizing the cardiac element at the earliest possible moment is further shown by the fact that involvement of this organ may develop soon after the primary infection without symptoms which attract attention until months or even years later.

The claim made by Landois, Citron,[4] Hausmann, Sears,[5] and others that lues may affect the heart alone is both interesting and important. In two infants who died, one at three months of inanition and the other at eight days of asphyxia, Warthin and Snyder found the Spirocheta pallida in the heart muscle, while neither histological lesions nor spirochetes were found elsewhere.

Among the commonest cardiovascular conditions due to syphilis are myocarditis, aortic regurgitation, angina pectoris, and mesaortitis, often resulting in aneurysm.

MESAORTITIS. Since mesaortitis, with or without coronary changes, is commonly the primary complaint in cases in which, as frequently occurs, two or more of the affections named above are found in association, it will be considered first in this paper. That this condition is due in many cases at least to syphilis has been demonstrated both by postmortem evidence and the results of carefully conducted therapeutic observations. In 1910 Longscope[6] pointed out that a peculiar type of arteriosclerosis (mesaortitis)

[2] Deutsch. Arch. f. klin. Med., 1900, lxvii, 455; 1901, lxviii, 58 and 264.
[3] AMER. JOUR. MED. SCI., October, 1913, p. 513.
[4] Berl. klin. Woch., 1908, xl, 2142.
[5] Archives of Diagnosis, January, 1913, p. 62.
[6] Jour. Amer. Med. Assoc., January 8, 1910, p. 118.

was frequently associated with aortic incompetency due to chronic aortic endocarditis. For example, in a series of thirty-seven autopsies showing mesaortitis a chronic aortic endocarditis occurred thirteen times, or in 35.1 per cent. Again, in 21 cases of chronic aortic endocarditis unassociated with lesions of any other valves occurring in connection with mesaortitis it was found that the lesions varied somewhat in extent in the individual instances, "but were always confined and often sharply localized to the arch of the aorta."

Of the 21 cases of aortic insufficiency associated with mesaortitis, 11 gave a definite history of either syphilitic infection or syphilitic lesion (gummata).

Harlow Brooks,[7] who made an anatomical study of the heart and aorta in fifty consecutive autopsies, found that 66 per cent., "including well and incompletely treated instances, died as a result of or with serious circulatory disease apparently of specific origin." Of these the myocardium was seriously involved in 44 cases, the coronaries in relatively greater degree than the general arterial system.

That this mesaortitis is of specific nature, with definite characteristics, is shown by the fact that the spirochetes have been found by Schmol and Wright in the lesions, the latter being able to demonstrate these organisms, often in enormous numbers, in all of five cases. Says Osler: "Microscopically the most important changes are found in the media and adventitia: (*a*) perivascular infiltration of the vasavasorum; (*b*) small-celled infiltration in areas of the media, with (*c*) splitting, separation, and destruction of elastic fibers and the muscle cells. The process is largely a productive mesaortitis, and so marked may be the foci in the adventitia and media that they look like miliary gummata, and, in fact, were so described as far back as 1877 by Laveran and by Heiberg."

ANEURYSM. The intimate connection between lues and aneurysm was well known to the older writers—to Pari, Larcisi, and Morgagni; but it has been specially emphasized by many modern writers, among whom the names of Osler, Heller, Koster, Chiari, Benda, and Klotz are conspicuous.

The belief that in persons under forty-five years of age syphilis plays the overshadowing role as an essential factor in causing aneurysm is confirmed by practically all of the more recent writers. On the other hand it may not be wholly gratuitous to caution the medical profession, as Hausmann has done, against regarding every case of aneurysm, even in syphilitic subjects, as due to lues.

Two additional facts may aid materially in distinguisbing the etiological variety of aneurysm under discussion, namely, that the root of the aorta, *i. e.*, the ascending portion of the arch, is the usual seat of luetic aneurysms, and that they are frequently multiple.

[7] Loc. cit.

Statistical evidence is not wanting to strengthen the view that syphilis is the most potent etiological factor in the production of aortic aneurysm. Cumston[8] quotes Rasch, of Copenhagen, who found twenty-eight aortic aneurysms in a series of 3165 autopsies. In 16 cases, or 57 per cent., syphilis was positively known to exist, while in 7 others, or 25 per cent., syphilis could be taken for granted in all probability. Etienne in a total of 240 cases of aneurysm found syphilis to be the cause in 166 cases, or 60 per cent. These figures have been amply confirmed by the following, among other percentages: Malmsten, 80; Heller, 85; Hampeln, 82; Pansini, 65.

My own collective investigations yielded a totality of 621 cases, of which number 363, or 58.5 per cent. were of luetic origin. In view of the fact that some of these cases had not been submitted to the Wassermann test, this percentage is too low. Among eight instances included in the above figures occurring in the Medico-Chirurgical Hospital, six were caused by lues.

A full discussion of the diagnosis of syphilitic thoracic aneurysm is not within the scope of this paper, but I desire to lay particular stress on a single fact bearing on this phase of the subject, namely, that a positive Wassermann reaction without confirmatory historical or clinical evidence (*e. g.*, age of the patient, site of the tumor-like protrusion, history of specific infection, etc.) does not warrant an assured diagnosis of lues.

Aortic Incompetency. Syphilis is now generally regarded as an essential factor in the causation of aortic incompetency, more particularly in cases which develop before the forty-fifth year of life. The chronic aortic endocarditis is commonly associated with mesaortitis, as before stated, affecting the root of the aorta, and, indeed, may be the result of direct involvement of the segments in such cases. It is worthy of note that this etiological variety of aortic incompetency is often met with unassociated with widespread arteriosclerotic changes. In this connection it should be stated that a pure mitral lesion is seldom produced by lues, but a combined aortic and mitral lesion is commonly caused by syphilis.

There is a consensus of opinion to the effect that the most important etiological factor in the production of aortic incompetency is luetic infection. This view is amply supported by statistical observations. Thus Longcope[9] in a series of thirty-seven autopsies showing mesaortitis found thirteen instances of chronic aortic endocarditis (35.1 per cent.). Again, of 21 cases of aortic insufficiency, 11 either gave a definite history of syphilis or syphilitic lesions were discovered at autopsy. Citron obtained a positive Wassermann reaction in 10 out of 16 cases of this cardiac lesion, or in 62.6 per cent. Fiessenger[10] obtained a history of syphilis in 28 out of 37 cases of

[8] Archives of Diagnosis, January, 1913, vi, 25.
[9] Loc. cit.
[10] Bull. de l'Académie de Médecine, October 10, 1911.

aortic insufficiency. Collins and Sachs[11] found a positive Wassermann reaction in 10 out of 13 instances of aortic valvular disease. Babcock[12] records 16 cases of aortic regurgitation, of which 11 were submitted to a Wassermann test with a positive reaction in all of the cases.

My own collective investigations into the question of the frequent association of aortic insufficiency and syphilis embrace a total of 219 cases inclusive of the figures cited above. Of these 133, or 60.7 per cent., were clearly due to lues. In a considerable number of the cases of aortic incompetency no reference to the Wassermann test was noted. Obviously then the above figures underestimate the true role of syphilis in the production of this condition.

Severe pains may attend an invasion of the valve segments often accompanied by angina pectoris from implication of the coronaries in early cases developing more or less acutely. If the specific character of the cause be overlooked an inappropriate or the usual routine treatment of chronic valvulitis be adopted these cases may reach an early fatal termination. On the other hand, intensive antisyphilitic treatment may, if instituted early, bring about marked improvement, and the cases progress as aortic incompetency due to other causes.

While a certain diagnosis of syphilitic valvulitis affecting the aortic segments can not be made without a clear history of either specific infection or a positive Wassermann reaction, supported by confirmatory evidence, yet in the absence of rheumatism, gout, lead, alcoholism, pyogenic infection, or a predisposing occupation such cases should be labelled suspects and given the benefit of vigorous antisyphilitic treatment. Obviously, in instances belonging to this group the Wassermann test should be carried out, whenever possible, before remedial measures are instituted.

There are a few special physical signs which aid in the establishment of the luetic character of the chronic valvulitis. For example, Sachs[13] points out that "enlargement of the left ventricle is generally not so marked as in other forms of aortic insufficiency, and, therefore, the capillary pulse and double sound over the crurales are not so marked." I have observed the presence of a more decided arrhythmia in cases of aortic incompetency due to syphilis than in those due to other causes.

The early recognition of the true nature of the lesion becomes a matter of much practical importance, to the end that the ravages of this disease may be, to a great extent at least, obviated by suitable treatment. In this connection it should be pointed out that congenital cases of this affection may be due to hereditary lues.

[11] Amer. Jour. Med. Sci., September, 1909, p. 344.
[12] Lancet-Clinic, August 15, 1912.
[13] Archives of Diagnosis, January, 1913, p. 62.

In cases in which the history is obscure too much stress can not be placed on the value of the Wassermann reaction as a means by which to determine the etiological variety in question. As in the case of aneurysm, so in aortic incompetency, a positive reaction alone unsupported by other clinical evidence does not warrant an assured diagnosis of lues, but it renders it highly probable that syphilis exists.

On the other hand it must be recollected that aortic incompetency occurring in a luetic subject may be due to causes other than syphilis, more especially if the valvular lesion develop after middle life. Here it should be noted that the cardiac lesions of syphilis usually appear within two or three years after infection, a fact of considerable diagnostic significance in some cases at least.

Myocarditis. As stated above, early involvement of the myocardium is not infrequent in the course of syphilis. Isaac Adler[14] first pointed out that the most important lesion of the heart is one of the myocardium, which lesion is dependent on periarteritis of the coronary vessels. Here it should be well understood that while endarteritis is the frequent important lesion, actual gummata in the myocardium are distinctly infrequent. Warthin[15] has described a syphilitic interstitial myocarditis in the absence of coronary periarteritis, and has demonstrated that the light-staining patches of proliferating stroma represent localized colonies of the spirochetes. Mareck, Simons, Buschke, and Fischer have also demonstrated the spirochetes in the diseased muscle of luetic myocarditis.

The recognition of incipient myocardial involvement is difficult, since the functional derangements thus produced are often slight, or, indeed, the condition may be entirely latent. The onset of the symptoms, if it develop in the secondary stage of syphilis, may be somewhat rapid or even acute. The principal features are arrhythmia, particularly intermittence and tachycardia, and less commonly extrasystoles. Brooks emphasizes among the earliest symptoms "irregularity of action, more marked when strain is added by mild exercises or through nervous apprehension;" he found the same thing true of the tachycardia, which is "incited to a degree by conditions which in the normal would fail to elicit such a response." Grassman writes: "I have studied 288 cases of secondary syphilis, and in 85 per cent. found disturbances of the rate and rhythm of the pulse, while in 40 per cent. accidental murmurs, usually with dilatation, occurred."

Pain is not a prominent feature, as a rule, in the early phases of the disease, although a feeling of thoracic oppression and slight dyspnea may be noted. In rare instances in which extensive

[14] Trans. Assoc. Amer. Phys., May 3, 1898.
[15] Amer. Jour. Med. Sci., March, 1912.

lesions are present, actual pain with more or less tendency to radiation may be observed. The symptoms enumerated do not differ from those due to the myocarditis of other infections than syphilis, and it has been shown that these indications may all disappear in the course of a few days as the result of energetic antisyphilitic treatment—a fact that emphasizes the importance of an early recognition of the condition.

In the tertian and quartenary stages of myocardial syphilis the symptoms and signs do not differ materially from those presented by myocarditis due to other causes. Not a few cases are latent and unsuspected during life, but are discovered if they come to autopsy. Soon or late in some cases dilatation is observed to occur, especially as the result of unwonted exercise, and this may be attended with a murmur.

Anginoid pains are not uncommonly present and obliterative endarteritis implicating the coronaries and producing myocarditis may result in attacks of true angina pectoris.

The markedly irregular character of the arrhythmia has been, as stated above, emphasized by Brooks, and his observation has been confirmed by my own experience. The observation first made by Runeberg, namely, tonelessness of the first sound at the apex, has since been confirmed by Callender[16] and others.

It is to be observed that neither a characteristic grouping of features nor a single pathognomonic symptom, unless it be a positive Wassermann reaction, are presented by the condition. As regards the Wassermann test it may be said that although a positive or negative reaction is not an absolute criterion of the presence or absence of a syphilitic infection, Brooks contends that it is better than the 70 per cent. of error based on the history or clinical findings alone.

Certain clinical peculiarities already mentioned may, however, serve to arouse suspicion of syphilis. Of these the tonelessness of the first heart sound and the decidedly irregular, accentuated character of the arrhythmia deserve special mention. Again, the association of phenomena which point to syphilitic involvement of other organs and structures of the body often throw light on the character of any cardiac lesion that may be present. Lastly, all determining causes of myocardial disease other than syphilis should be carefully excluded.

Heart-block is frequently caused by syphilitic lesions of the bundle of His, but this phase of cardiac lues can not be enlarged upon here. Suffice it to cite the figures of Robinson, who found that among 16 cases of heart-block due to such lesions 6 at least were of syphilitic origin.

[16] Amer. Jour. Med. Sci., November, 1914, 706.

ANGINA PECTORIS. The writer has collected 270 cases of angina pectoris from the literature, of which only 72, or 26.5 per cent. gave evidence of syphilis. This percentage, however, is much too low, since in 250 of the recorded instances no mention was made of a Wassermann test, sole dependence being placed in the history. The close association of syphilis and angina is amply confirmed by modern authorities. Breitmann,[17] of St. Petersburg, writes: "Every case of angina pectoris during the younger period of life is open to the suspicion of syphilitic origin." R. O. Moon[18] has been much impressed with the great predominence of lues in connection with true angina, and has seldom met with a case since the advent of the Wassermann test which did not give a positive reaction. Saundby[19] states that congenital syphilis as a cause of angina pectoris is not to be overlooked in young patients.

PROPHYLAXIS. My discussion of the treatment of cardiovascular syphilis will be, owing to the exigencies of time and space, limited to prophylaxis. Doubtless the incidence of cardiovascular disease would be much lessened by a more systematic and vigorous treatment of luetic infection in general. There is perfect unanimity among syphilographers and clinicians of wide experience regarding the belief that when either syphilis of the myocardium of marked extent or aortic incompetency exists a cure is impossible of attainment.

Physicians should, therefore, feel themselves charged with a serious responsibility on behalf of the victims of luetic infection and carry out the treatment of early syphilis in the wisest manner possible. An added reason for adopting this course lies in the hazard arising from the administration of salvarsan or neosalvarsan in the severer forms of cardiovascular syphilis. It has been found that death, either occurring suddenly or after several days from the use of these agents, is commonly due to myocardial degeneration secondary to coronary lesions.

As stated elsewhere, "A sane view of the prophylaxis of cardiac involvement in this disease demands inclusion of the treatment of its secondary manifestations." It is in this stage that its development may take place, and also that the time of cardiac invasion can be fixed by the appearance of certain clinical features, in some cases at least.

In concluding the writer desires to make grateful acknowledgment of the assistance rendered by Drs. H. Leon Jameson and Andrew A. Anders in the work of searching the literature in connection with these statistical investigations.

[17] Quoted by Bruce, Lancet, London, 1911, ii, 69.
[18] Clin. Jour., London, 1912–1913, xli, 353.
[19] Ibid., May 21, 1913.

A REPORT OF THREE HEART CASES SHOWING VAGUS INFLUENCE.

By Montgomery H. Sicard, M.D.,

and

Frank S. Meara, M.D.,

new york city.

(From the Department of Therapeutics, Cornell University Medical College.)

The three cases presented here occurred in the wards of the second (Cornell) division of Bellevue Hospital, and showed such points of common interest that they may well be grouped together.

Case I.—Sinus block, standstill of the heart. By these terms is meant a condition not only of skipped pulse and apex beats, but a dropping out of the whole cardiac cycle, either occasionally, frequently, or in sequence; periods of standstill[1] may be several seconds in duration.[2] It occurs as a result of vagus stimulation either by drugs (such as the digitalis series), by digital pressure, or by severe athletic exercise. Our purpose is to show that it is also produced by salicylic acid.

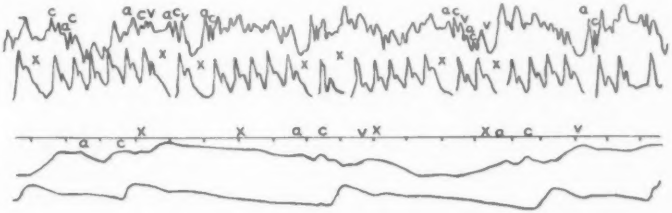


Fig. 1.—Sinus block induced by sodium salicylate. The tracings are from the same individual, and represent the same events; in the lower tracing the paper was moving faster, to draw out the curves for greater facility in reading.

Two years ago a woman came into the hospital in September, having taken salicylates during the entire summer; her pulse showed dropped beats which might well have been taken for ordinary intermissions or premature systoles; her apex also showed dropped beats which corresponded with the pulse intermissions; a tracing showed standstill of the whole heart during these periods. No other case came under observation until the present season, when a young man was admitted who was suffering from acute rheumatic

[1] Mackenzie, Diseases of the Heart, 1908, p. 345.

[2] Laslett, E. E., Syncopal Attacks Associated with Prolonged Rest of the Whole Heart, Quart. Jour. Med., 1908–9, ii, 347.

fever, and who later developed endocarditis, pericarditis, and bronchopneumonia. His treatment consisted of salicylate of soda (20 grains every two hours for nine days), followed by tincture of digitalis (30 minims every four hours) for five days; a drop in pulse rate to 58 ensued, which disappeared when the digitalis was stopped. After a rest of four days, sodium salicylate (20-grain doses every two hours) was begun and continued for nine days, when block set in, to disappear after discontinuing the drug.

The upper tracing shows normal *a–c* intervals, and shows also the lengths and frequency of the periods of standstill. The lower tracing shows one normal cycle followed by two successive periods of standstill, then two normal cycles; the *a–c* intervals are present and normal with each heart beat, and no event whatever occurs in the jugular tracing during the period of prolongation, showing that no impulse was generated at the sinus node. The resumption of rhythm in every instance here is normal; cases are reported in which slowing and irregularity are observed, the ventricles sometimes escaping first by premature systole.

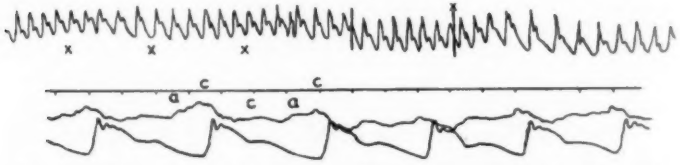


FIG. 2.—Effect of vagus pressure on a rapid heart; (the second tracing is normal and does not show the effect of pressure).

CASE II.—Increased heart action, normal in origin (sinus node), controlled by vagus pressure.

V. S., a man, aged fifty years, in previously good health, noticed upon exercise a little palpitation and an increase in pulse rate to 116; he was told by a consulting neurologist that he had heart block; physical examination showed nothing, however, but the increased rate on exertion and a sinus irregularity; there was no evidence of block. A sinus arrhythmia is evident; impulses are of normal origin and propagation was shown by the normal *a–c–v* intervals; the increased rate is noticeably slowed by right vagus pressure, but it immediately, though not suddenly resumes, its former rhythm upon removal of pressure; left vagus pressure shows no change in rhythm.

CASE III.—Paroxysmal tachycardia controlled by vagus pressure. Patient was a man, aged fifty-three years, who for two and a half months had had moderate edema, slight cyanosis, and dyspnea. Physical examination showed cardiac enlargement, with mitral leakage, increased blood-pressure, albumin and a few casts

in the urine. He knew nothing about his paroxysms, and the first one came on after the exertion of sitting up in bed for examination.

The first tracing starts with normal rate and normal *a–c–v* intervals; the third beat is a premature systole; the fifth beat initiates the onset of the paroxysm, and the previous *a–c* sequence is now reversed to a *c–a* rhythm. The explanation is that with the onset of the paroxysm the auricular contraction falls back upon the preceding ventricular contraction and coincides with it, and this is true for every beat as long as the paroxysm lasts; in other words, the paroxysm is a series of premature auricular systoles. The paroxysm stops as suddenly as it begins, but the tracing has not caught the ending of it. The second tracing shows the paroxysm and normal period in fast time, but not in sequence.

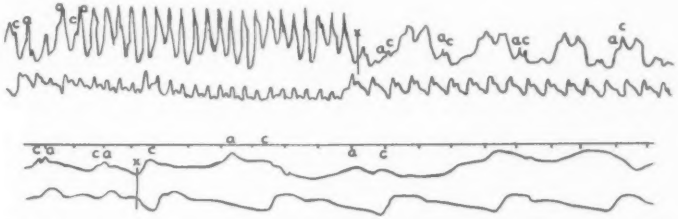


FIG. 3.—Paroxysmal tachycardia of auricular origin; the tracings show both the tachycardia and the normal period of action, in both the slow and fast time.

Pressure upon the right vagus produced no result after numerous trials; pressure on the left vagus caused the paroxysm to cease in three or four seconds, and never failed to produce this result; normal action lasted, however, but a minute or less, when the tachycardia gradually (not suddenly) returned; it again slowly disappeared, with pressure on the left vagus. The paroxysms lasted over a period of a few days, when they disappeared altogether.

DISCUSSION. Pressure on the vagi has been frequently tried and often reported, but with variation in the results obtained. Lewis[3] has thought the pressure effects to be so irregular as to be unsatisfactory; he cites a case of 4-to-1 heart-block in which right vagus pressure stopped the ventricle altogether, and a case where left vagus pressure slowed the whole heart.

Cohn[4] helped matters greatly when he found (1912) that the right vagus is distributed mostly to the sinus node, sends a few fibers to the auricle, a few to the junctional tissue, and a few to the ventricle. The left vagus is distributed to the auriculoventricular node, sending a few fibers to the auricle, a few to the junctional

[3] Mechanism of the Heart Beat, p. 259.
[4] Effects of Stimulation of Vagi, Jour. Exper. Med., 1912, xvi, 732.

tissue, and a few to the ventricle. Cohn[5] thinks the auricles are always affected by right vagus stimulation, and the ventricles may also be affected either primarily or secondarily; the ventricles are controlled by left vagus stimulation while the auricles may or may not be affected.[6]

Robinson and Draper[7] studied the pressure effects on four children with endocarditis. Right-sided pressure slowed the rate of the heart-beat sometimes to such an extent that the ventricles assumed a rhythm of their own. Left vagus pressure controlled the rate of stimulus conduction. These results were the same as those obtained upon dogs, for Robinson[8] found that cutting the left vagus and stimulating the right stopped the whole heart; cutting the right and stimulating the left slowed but did not stop the auricles, but did produce increased difficulty in transmitting impulses from auricle to ventricle, so that heart-block resulted in varying degrees.

Conclusions. Case II of the series presented in this paper, a case of simple increased frequency of the heart's action, was controlled and slowed by compression of the right vagus governing the sinus node, the slowed impulses from which were transmitted through junctional tissue to the ventricles, maintaining normal rhythm; this is what one would expect.

Case III, tachycardia of auricular origin, was slowed by compression of the left vagus. Why was not this influenced by right vagus pressure as was the former one, both being of auricular origin? The answer must be found in Robinson's statement[9] that each nerve has to a lesser degree the function which predominates the other. Whether the ventricles were affected first, the auricles falling in line, or whether the subordinate fibers running to the auricles were first stimulated, the ventricles following by sequence, we have no way of knowing; the latter reasoning is the most likely one, as the paroxysm was not of ventricular origin, this being rare under any conditions.

[5] Auricular Tachycardia, with a Consideration of Differences Between the Vagi, Jour. Exper. Med., 1912, xv, 49.

[6] Cohn and Fraser, Paroxysmal Tachycardia and the Effect of Stimulation of Vagi Nerves by Pressure, Heart, v, No. 1.

[7] Action of Vagus Nerve on Human Hearts, Jour. Exper. Med., 1911, xiv, 217; 1912, xv, 14.

[8] Influence of Vagus Nerve on the Dog's Heart, Jour. Exper. Med., 1913, xvii, 429.

[9] Loc. cit.

THE "SUGAR" CONTENT OF THE SPINAL FLUID IN MENINGITIS AND OTHER DISEASES.

By Arthur H. Hopkins, M.D.,

INSTRUCTOR IN MEDICINE AND IN PRACTICAL THERAPEUTICS, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

(Under the J. Alison Scott Research Fund. From the William Pepper Laboratory of Clinical Medicine, University of Pennsylvania.)

The growing interest in and investigations of the origin and function of the spinal fluid have led to the study of this phase of the question, namely, the carbohydrate content or reducing substance of this fluid. The question is not only of theoretical interest in regard to the origin of the fluid and its relation to the blood serum, but also it is of definite practical value from the standpoint of early diagnosis and prognosis in meningitis and possibly in syphilis.

Repeated and exhaustive studies have been made of the physical, chemical, and biochemical properties of the spinal fluid in health and disease, and while attention has been given to the quantitative analyses of albumin, globulin, urea, etc., but little notice has been taken of the actual amount of the reducing substance. Tests, including Fehling's, Williamson's, Trömmer's, phenylhydrazin, fermentation, etc., have been utilized, the results in the hands of different workers being by no means of one accord; however, the conclusions of those who have made the most careful and prolonged studies indicate that this substance is chiefly glucose, though mucinoid matter, pyrocatechin, etc., may be present (Mestrezat,[1] Quincke,[2] Nawratzki,[3] Connal,[4] von Jaksch,[5] Trerotoli[6]). A few authors have made quantitative analyses over a limited number of cases, the results of which are variable and the estimations too few to be of real value.

Von Jaksch in 20 normal cases found 0.06 to 0.08 per cent.; Nawratzki, using Allihn's method, found 0.046 per cent.; Kopetzky,[7] with Benedict's method in 8 cases, found an average of 0.046 per cent. Mestrezat gives a table of all the constituents of both the spinal fluid and blood serum in 20 cases, the average concentration of the reducing substance of the fluid being 0.048

[1] Jour. de Phys. et de Path. gén., 1912, No. xiv, pp. 504–508.
[2] Quoted by Neuberg (note 8.)
[3] Zur Kenntnis der Zerebrospinalflüssigkeit, Ztschr. physiol. Chem., 1897, Bd. xxiii.
[4] The Cerebrospinal Fluid, Quart. Jour. Med., 1909–10, No. 3, p. 152.
[5] Klinische Diagnostik innerer Krankheiten, 5th Aufl., 567.
[6] The Spinal Fluid in Nephritis, Ann. d. facolta di Med., 1913, Bd. iii, Nr. 3, S. 101–324.
[7] Zeitschr. f. Ohrenheilk. u. f. d. Krank. d. Luftweg, 1913, Bd. lxviii, H. 1, S. 1–19.

to 0.053 per cent., and from these findings he supports the dialysis theory of the origin of spinal fluid, believing that beside the secretion there is a dialysis of blood plasma by means of epithelial differentiation, the constituents of both fluid and blood being so similar. My results in a series of normal cases reveal values of from 0.06 to 0.075 per cent., thus confirming the findings of von Jaksch and to a certain extent of Neuberg,[8] but being considerably higher than the values in the few cases given by the other workers.

The Relation of Blood Sugar to Spinal Fluid Sugar. In regard to the relation between blood sugar and the sugar content of the spinal fluid, Neuberg states that the content is the same in both. Using the same method (Bang's) for the estimation of the sugar content of both, I have found that in health the concentration in the blood averages about 10 mgm. per 100 c.c. higher than that of the fluid. This is of interest when we recall the studies of Goldmann,[9] who, by means of intravital staining, in his experiments upon the fetal nervous system of animals, discovered that intracellular glycogen was demonstrable only in the plexus cells. This substance, unlike the dye, was not held back by the cells but secreted drop by drop and diffused with the cerebrospinal fluid throughout the entire nervous system. Yoshimura[10] also demonstrated glycogen in the vacuoles of the epithelial cells of the choroid plexus. These discoveries when considered with those of Mott,[11] Pettit and Girard,[12] Dixon and Halliburton,[13] Frazier and Peet,[14] etc., present very forcible arguments in favor of the secretory origin of the fluid. They likewise bear convincing evidence of the presence of glucose in the spinal fluid, for until recently many have maintained that other substances than glucose were responsible for the reduction of copper.

In meningitis investigators have shown, as have I in a recent article,[15] that the blood sugar is considerably increased. On the other hand the sugar content of the fluid is materially decreased. It may be possible that the hyperglycemia in this disease is accompanied by an initial increase in the sugar content of the spinal fluid and that this latter increase is more than offset by the destructive activity of the organisms present, a condition which will be referred to later. The hyperglycemia in the majority of other disease in

[8] Der Harn sowie die übrigen Ausscheidungen und Körper'Flüssigkeiten, ii Teil, Berlin, 1911, S. 1019.

[9] Experimentelle Untersuchungen über die Function der Plex. Choroid. und der Hirnhaüte, Arch. f. klin. Chir., 1913, ci, No. 3, S. 735.

[10] Arbeiten aus dem Neurolog. Instit. d. Wiener Univ. (Obersteiner-Hefte), Bd. xviii.

[11] Quoted by Frazier and Peet (note 14).

[12] Ibid.

[13] Journal of Physiology, 1913, vol. xlvii, No. 3, pp. 215–224.

[14] Amer. Jour. Physiol., 1915, vol. xxxvi, No. 4.

[15] Hopkins, A. H., Studies in the Concentration of Blood Sugar in Health and Disease, Amer. Jour. Med. Sci., February, 1915, No. 2, vol. cxlix, p. 254.

which I have had an opportunity of studying simultaneously the blood and spinal fluid has usually been accompanied by a corresponding rise in the sugar content of the fluid, the figures being almost constantly somewhat lower in the fluid than in the blood.

Table I illustrates the variations that may occur in this relationship in disease.

TABLE I.—TABLE ILLUSTRATING THE VARIATIONS IN THE RELATION OF THE SUGAR CONTENT OF THE SPINAL FLUID TO THAT OF THE BLOOD IN DISEASE

Case.	Name.	Diagnosis.	Reducing substances in spinal fluid.	Blood sugar.
1	Ell.	Hemiplegia; apoplexy	0.078	0.169
2	Carr.	Subarachnoid hemorrhage	0.075	0.182
3	Hub.	Brain tumor	0.081	0.085
4	T.	Pituitary tumor (?)	0.074	0.077
5	Don.	Brain tumor (?)	0.070	0.080
6	Ke.	Syphilis	0.034	0.070
7	F. J.	Syphilis	0.053	0.085
8	Sp.	Syphilis; tabes	0.047	0.088
9	B. R.	Tuberculous meningitis	0.029	0.092
10	Dd. T.	Tuberculous meningitis	0.027	0.139
11	D.	Diplococcic meningitis	0.015	0.080
12	Ca.	Idiot; castration	0.085	0.105
13	D. S.	Idiot; castration	0.087	0.102

TECHNIC. The method employed is a slight modification of Bang's[16] recent micromethod for the determination of blood sugar, this having proved to be very useful as a rapid and reliable clinical test.

As only three or four drops of fluid are needed it affords possibilities for the study of practically every fluid withdrawn, and at the same time gives accurate results as the protein content of the fluid is thoroughly separated before the reduction of copper takes place.

The disadvantage of Fehling's test as at present used in many laboratories is that in fluids in which the protein content is high the reduction of copper is masked by the biuret reaction, and entirely erroneous results are thus not infrequently derived in the very cases in which the quantity of reducing substance is of most importance, as in meningitis. Further, the results are also unreliable if no definite amounts of the alkaline and copper solution are used and if the amount of dilution is not carefully regulated. Varying amounts of dilution give varying results, so that I have tried to establish a uniform method by controlling Fehling's with accurate quan-

[16] Der Blutzucker, Wiesbaden, 1913; Bioch. Ztschr., November, 1913, H. $\frac{3}{4}$, B. 57. Two or three drops of the fluid are taken up on the small specially prepared and weighed filter papers, the rest of the technique being carried out as described by Bang in his monograph, "Der Blutzucker." The only modification which I have used has been the subtraction of 0.07 c.c. from the amount of iodine required in the titration for the quantity of reduced copper. Bang in his test for blood sugar subtracts 0.12 c.c. from the iodin titration, claiming that the copper and alkaline solution neutralize 0.06 and that other substances than glucose in the red blood cells require another 0.06. In testing my copper and alkaline solutions, I found that 0.07 c.c. iodin was required, and hence that amount was subtracted.

titative estimations. In the majority of cases the Fehling test was applied at the time of Bang's test, and after using different dilutions I found that 1 c.c. each of the copper and of the alkaline solutions diluted with water to 15 c.c. and the addition of exactly equal parts of this solution and the fluid gave fairly constant relative results in all cases in which there was not a great increase in protein content. In the latter cases the results were not so clear cut, owing to the deep purple biuret reaction. The fermentation test was used in a few cases with positive results while the controls by Benedict's[17] new colorimetric method, for which I am indebted to Dr. G. K. Strode, are given in Table II. Estimations were made over a series of 141 cases of various diseases, in a number of which the blood sugar concentration was studied at the same time.

TABLE II.—ILLUSTRATING THE CONTROL OF BANG'S METHOD WITH BENEDICT'S COLORIMETRIC METHOD.

Case.	Bang.	Benedict.
1	0.087	0.086
2	0.066	0.065
3	0.071	0.099
4	0.068	0.061
5	0.066	0.052
6	0.116	0.134
7	0.084	0.077
8	0.062	0.044
9	0.053	0.058
10	0.027	0.000
11	0.107	0.115
12	0.104	0.116

MENINGITIS. The early diagnostic and prognostic value of the test for glucose in the spinal fluid has been emphasized by many. Sicard and Roussea,[18] Silvestrini and Nestri,[19] Mestrezat, Kopetzky, Connal, Jacob,[20] etc., found it markedly reduced in meningitis. Kopetzky remarks upon the necessity of sugar as a medium for the growth of many bacteria and that the prompt examination of the spinal fluid in suspected cases of meningitis is specially urgent, as it is generally known that with bacterial invasion of the meninges there is a rapid reduction in the glucose of the fluid, and hence the earliest and most important clue may be given by the discovery of a reduction of glucose, a view supported by Connal, Kaplan, and others. Accepting these findings and confirming them by my results in quantitative analyses of twenty cases it is evident that the test is of practical value in distinguishing between meningitis and the so-called "meningismus" accompanying pneumonia, typhoid fever, etc.

[17] Jour. Phys. Chem., October, 1914.
[18] Quoted by Trerotoli, A., Note 6.
[19] Ibid.
[20] British Med. Jour., 1912, p. 1096.

From the prognostic standpoint it has been found that as the bacteria loose their virulence and their ability to break up sugar and as they become more difficult to cultivate from the fluid, the sugar content gradually increases and is in turn followed by convalescence. This increase may be ascertained by repeated lumbar punctures even before clinical improvement has been observed, and hence its value as the earliest sign of improvement. Investigators have evidently overlooked the fact that the injection of Flexner's serum in the treatment of this disease is probably responsible for the immediate rise in the reducing substance. I find that this serum is higher in its sugar content than normal blood serum, the average being 0.11 per cent., a figure considerably higher than that of the normal spinal fluid. Table III illustrates the results in a series of cases of meningitis. As these fluids were contributed from the laboratories of various hospitals it has not been possible to make simultaneous studies upon the blood sugar in many instances.

TABLE III.—MENINGITIS.

Case.	Name.	Diagnosis.	Reducing substance.
1	Bl.	Tuberculous meningitis	0.035
2	Bl.	" "	0.048
3	E. G. Mc.	" "	0.037*
	E. G. Mc.	" "	0.038
4	B. R.	" "	0.046
5	F. E.	" "	0.017
6	C. W.	" "	0.020
7	F. C.	" "	0.023
8	D. D. T.	" "	0.032*
	D. D. T.	" "	0.027
9	B. R.	" "	0.035*
	B. R.	" "	0.019
10	D. F.	" "	0.046
11	D. G.	" "	0.033
12	J. W.	" "	0.033
13	A. Y.	" "	0.037
14	A. E.	" "	0.066*
	A. E.	" "	0.053
15	Mc.	" "	0.027*
	Mc.	" "	0.030
16	Dr. T.	" "	0.020
17	Da.	Diplococcic meningitis	0.015
18	J. C.	Pnemococcic meningitis	0.016
19	A. D. P.	Acute meningitis	0.008
20	Mac	Acute meningitis	0.048
21	J. R.	Acute meningitis	0.018
22	R. S.	Diplococcic meningitis	0.031
	R. S.	Diplococcic meningitis	0.079†

* Values obtained on different dates.

† Twenty-four hours after the administration of Flexner's serum.

The results show consistently low figures, which in a few instances were repeated at different dates. It should be noted that Fehling's reaction, though slight, was not altogether absent, although fre-

quently considerably masked by a strong biuret reaction, owing to the increased protein content.

DIABETES. This series of diabetes (Table IV) gave interesting results, as there was a striking increase in the sugar content of the fluid which, however, usually remained lower than that of the blood.

TABLE IV.—DIABETES.

Case.	Name.	Reducing substance in spinal fluid.	Blood sugar.
1	U.	0.163	0.187
2	G.	0.149	0.221
3	K.	0.131	0.169
4	B.*	0.623	0.660
5	P.	0.174	0.223
6	M.	0.187	0.174
7	McM.	0.112	0.134
8	T.†	0.074	0.077

* In coma five hours before death.
† Glycosuria persistent.

The reduction of Fehling's solution was, as a rule, complete when the dilution was 1:15, but in other dilutions the reactions were variable, though always marked. In the few cases mentioned by other investigators an increase in the sugar content has been noted, Fehling's qualitative test being the one employed.

INFECTIONS. In this short series (Table V) the values lie approximately within normal limits and require no comment other than a reference to the recent paper of Rohdenburg and Vander Veer[21] on the question of spinal fluid in pneumonia. Being impressed with the mental depression so often encountered in this disease, they made a chemical and bacteriological study of the spinal fluid in a series

TABLE V.—INFECTIONS.

Case.	Name.	Diagnosis.	Reducing substance.
1	G. H.	Measles	0.063
2	D. M.	Pneumonia	0.061
3	Ger.	Pneumonia	0.063
4	J. C.	Pneumonia; dementia precox	0.063
5	C. W.	Bronchopneumonia; nephritis	0.085
6	Vet.	Poliomyelitis	0.077
7	R. B.	Septicemia; nephritis	0.036
8	M. M.	Septicemia; pyelitis	0.116
9	C. S.	Pulmonary tuberculosis	0.057
10	T. M.	Articular rheumatism	0.080
11	Rei.	Tetanus	0.077

of cases irrespective of the occurrence of meningeal symptoms and in which only one case showed pure meningitis. Of the fatal cases, 87 per cent. showed pneumococci in culture, while in those of favorable termination 34 per cent. gave positive cultures. They further state that all fluids giving positive cultures were positive

[21] The Spinal Fluid in Pneumonia, Jour. Amer. Med. Assoc., 1915, No. 15, vol. lxiv.

for both sugar and globulin, but as no reference is made as to the method employed for the sugar determinations the relative variations are lost. These authors conclude that pneumococci are very frequently present in the spinal fluid in pneumonia and that the early lysis of these organisms, with the liberation of the endotoxin in close proximity to the vital centres, offers a ready explanation of the profound and sudden cardiovascular collapse as well as the mental symptoms of the disease so often noted, for in patients in which positive cultures were obtained from the fluid, profound depression and frequently delirium were noted.

INTOXICATIONS. In this series (Table VI) morphin did not influence the sugar content; alcoholism gave inconstant results. Case 6, being one of delirium tremens, showed a pronounced increase. Case 7, acetanilid poisoning, was studied a few hours before death. The low value obtained in Case 8, atropin poisoning, is interesting in view of the secretory theory and of the possible action of atropin upon the choroid plexus, though Dixon and Halliburton state that atropin does not check the secretion in dogs when administered in the usual size doses.

TABLE VI.—INTOXICATIONS.

Case.	Name.	Diagnosis.	Reducing substance
1	McD.	Morphinism	0.073
2	J. S.	Morphinism and heronism	0.075
3	B. D.	Alcoholism	0.096
4	G. B.	Alcoholism	0.056
5	J. C.	Alcoholism	0.071
6	E. B.	Alcoholism and delirium tremens	0.129
7	A. E.	Acetanilid poisoning	0.139
8	J. S.	Atropin poisoning	0.057
9	H. B.	Alcoholism; arteriosclerosis	0.073
10	A. T.	Alcoholism; cirrhosis of liver	0.050

NEPHRITIS. Trerotoli, in his exhaustive monograph on the *Spinal Fluid in Nephritis*, considers that the influence of renal impermeability is mirrored by the chemical composition of the spinal fluid. He notes the importance of the increased urea content specially as a sign of impending uremia, a fact recently recalled by Soper and Granat,[22] who also emphasize the value of quantitative estimations for both diagnostic and prognostic use. Mestrezat, in a few cases of uremia, reports an increase in the sugar content of the fluid.

In this series of 14 cases, several of which were complicated by other conditions, 7 cases gave high values, 6 of the latter being uremic and in these the blood sugar, when estimated, also revealed an increased concentration. Here it must be recalled that a moderate hyperglycemia occurs in some hypertension nephritics. From

[22] The Urea Content of the Spinal Fluid, with Special Reference to its Diagnostic and Prognostic Significance, Arch. Int. Med., 1915.

the low value in Case 13 I suspect meningeal involvement, as the case was complicated by a septicemia. Although Case 5, uremia, had been receiving a 5 per cent. glucose solution by rectum for fourteen hours the content of glucose in the fluid was not unusually high (Table VII).

TABLE VII.—NEPHRITIS AND UREMIA.

Case.	Name.	Diagnosis.	Reducing substance in spinal fluid.	Blood sugar.
1	C. B.	Uremia	0.104	—
2	R.	Uremia	0.127	0.149
3	M. L.	Uremia	0.072	0.127
4	Ba.	Uremia	0.093	0.144
5	K.	Uremia	0.089	—
6	A. A.	Uremia; acute parenchymatous nephritis	0.084	
7	G. W.	Uremia	0.092	
8	J. McV.	Acute parenchymatous nephritis	0.072	0.087
9	Ne.	Chronic interstitial nephritis; syphilis	0.068	0.073
10	C. W.	Nephritis; pneumonia; parotitis	0.139	—
11	N. S.	Chronic nephritis; myocarditis; post. sclerosis	0.073	0.088
12	S. L.	Chronic nephritis	0.060	—
13	R. B.	Nephritis; septicemia; sub-deltoid abscess	0.036	—
14	D. R.	Chronic nephritis	0.059	

EPILEPSY. Boyd[23] found Fehling's test very positive in four epileptic insanities, while Thabius and Barbé[24] and Karpas[25] report negative results in their physicochemical studies in epilepsy.

These 14 cases were studied without regard to proximity of convulsions or of the type of the epilepsy. Half of the cases showed a moderate increase in reducing substance, the other half were normal, while the blood sugar concentration was slightly increased in 4 out of 6 cases (Table VIII).

TABLE VIII.—EPILEPSY.

Case.	Name.	Reducing substance.	Blood sugar.
1	J. H.	0.081	0.125
2	J. C.	0.067	
3	H. C. M.	0.093	0.100
4	E. McG.	0.094	0.118
5	L.	0.076	
6	G. H.	0.086	0.080 (vein)
7	McD.	0.063	0.063
8	M. G.	0.084	
9	M. A.	0.051	
10	E.	0.077	0.117
11	M. M.	0.100	
12	F. S.	0.066	
13	A. P.	0.074	
14	G. G.	0.084	

[23] The Cerebrospinal Fluid in Certain Mental Conditions, Jour. Ment. Sci., 1912, No. 58, p. 203.

[24] La composition physico-chemeque du liquide céphalo-rachidien des epileptiques, Rev. Neurol. Jg., 1913, xxi, Nr. 17, S 248–253.

[25] Amer. Jour. Insanity, 1912–13, lxix, 143.

VARIOUS NERVOUS DISEASES. In a series of 33 cases of various mental and nervous disorders the only cases revealing abnormal figures were the hemiplegias, half of which were high, one case of hypomania also high, and one case each of melancholia and of suspected brain tumor, both of which were very low (Table IX).

TABLE IX.—NERVOUS DISEASES.

Case.	Name.	Diagnosis.	Reducing substance in spinal fluid.
1	G. F.	Hemiplegia	0.105
2	E. H.	Hemiplegia	0.073
3	L. B.	Hemiplegia	0.100
4	V. O.	Hemiplegia (arteriosclerotic)	0.092
5	F. M.	Hemiplegia	0.074
6	B. W.	Hemiplegia	0.086
7	McC.	Hemiplegia (cancer)	0.065
8	El.	Hemiplegia (cerebral hemorrhage)	0.078
9	Car	Subarachnoid hemorrhage	0.075
	"	" "	0.105
10	M. B.	Senile dementia	0.093
11	J. W.	Dementia precox	0.066
12	J. C.	Dementia; pneumonia	0.060
13	G. B.	Hypomania	0.171
14	Hb.	Brain tumor	0.081
15	A. C.	Brain tumor	0.061
16	J. U.	Brain tumor	0.070
17	R.	Brain tumor	0.071
18	V.	Tumor of cord	0.063
19	J. R.	Brain tumor	0.025
20	T.	Pituitary tumor (?)	0.074
21	N.	Optic atrophy	0.062
22	P.	Brain abscess	0.081
23	M. T.	Cord lesion	0.078
24	N. S.	Posterior sclerosis	0.073
		Nephritis; myocarditis	
25	J. H.	Transverse myelitis	0.064
26	N. D.	Multiple sclerosis	0.074
27	Gr.	Primary lateral sclerosis	0.073
28	C. P.	Muscular sclerosis	0.078
29	P. C.	Progressive spinal muscular atrophy	0.067
30	C. A.	Idiot; castration	0.085
31	D. S.	Idiot; castration	0.087
32	V. N.	Sciatica	0.063
33	Wh.	Melancholia	0.048

SYPHILIS. The values here were so frequently low that they deserve attention (Table X), only 9 out of 29 cases falling within the normal limits. In 3 of the cases the blood sugar was normal, and it may be added that this is the only group of cases other than the meningitis series in which the sugar content of the fluid and blood did not usually run *pari passu*.

Kaplan[26] in a study of the differentiation of paresis and cerebrospinal syphilis found in untreated cases of general paresis that Fehling's reaction was always positive while in cerebrospinal syphilis

[26] Laboratory Difference between General Paresis and Cerebrospinal Syphilis and Serology of Spinal Cord Tumors, Amer. Jour. Insanity, 1912–13, lxix, 336.

it was sometimes absent. Here the increased protein content evidently influenced the reduction of the copper; under treatment, however, the reaction returned in the cases of cerebrospinal syphilis.

Shortly before the completion of this work an article was published by Biach, Kerl and Kabler[27] on the question of changes in the spinal fluid after the administration of neosalvarsan. These investigators also used Bang's method for determining the reducing substance.

TABLE X.—SYPHILIS.

Case.	Name.	Diagnosis.	Reducing substance.
1	M.	Tabes	0.071
	M.	Tabes	0.066
2	Tr.	Tabes	0.086
	Tr.	Tabes	0.064
3	I. H.	Tabes	0.069
4	Sp.	Tabes	0.049
5	McD.	Tabes	0.051
6	N. S.	Tabes	0.068
7	A. H.	Tabes	0.080
8	H. W.	Tabes	0.056
9	P. F. Y.	Tabes	0.044
10	Sh.	Tabes (?)	0.088
11	McL.	Tabes (?)	0.079
12	A. R.	Cerebral syphilis	0.052
13	Hor.	Cerebral syphilis	0.065
14	N. L.	Cerebral syphilis	0.038
15	G. G.	Cerebral syphilis (?)	0.084
16	Ne.	Cerebral syphilis (?)	0.055
17	E. A.	Bone lesions	0.083
18	J. J.	Periostitis	0.039
19	F. J.	Skin lesions	0.053
20	Wei.	Syphilis	0.068
21	N. H.	Syphilis	0.056
22	J. M.	Syphilis	0.052
23	Bl.	Syphilis	0.069
24	FO.	Syphilis (?)	0.056
25	Th.	Syphilis (?)	0.060
26	R. B.	Syphilis (?)	0.052
27	P. S.	Syphilis (congenital)	0.066
28	Ke.	Syphilis	0.038
	Ke.	Syphilis	0.042
29	Pr.	Syphilis (?)	0.053

Their series consisted of 14 untreated cases of syphilis, in which they found values varying from 0.04 to 0.09 per cent., and 12 cases treated with neosalvarsan with a resulting marked rise in the sugar content, one case reaching 0.34 per cent. Unfortunately the same patients were not used in studying the fluid before and after treatment, nor was the blood sugar estimated. They state that changes in the sugar content are not associated with any definite symptoms. As an explanation for the marked rise after the drug they suggest the possibility of renal impermeability and the fact that the neosalvarsan passes into the spinal fluid

[27] Zur Kenntnis der Veränderungen der Spinal Flüssigkeit nach Neosalvarsan applikation, Wien. klin. Woch., 1914, No. 30, p. 1098.

and is capable of reducing copper, and finally they quote Hess and Pohl, who believe that ferment action is responsible for the change as a result of destructive processes in the brain tissue.

This question will not be dealt with further, as investigations involving this and other phases of the fluid in syphilis are being carried out in conjunction with Drs. Laird and Jonas.

SUMMARY AND CONCLUSIONS. The consensus of opinion, based on recent literature, is that glucose is the principal reducing substance in the spinal fluid. Its concentration in health is slightly lower than that of the blood sugar, as shown by these studies in which Bang's method was used for both.

In meningitis there is the greatest disturbance in this relationship, there being a pronounced hyperglycemia associated with just as pronounced a drop in the sugar content of the fluid, this drop being due evidently to the destructive activity of the invading micro-organisms.

In diabetes the sugar content of the spinal fluid is almost as high as that of the blood. In infections such as pneumonia there may be a hyperglycemia without apparent change in the spinal fluid. The reducing substance of the fluid is frequently increased in uremia, a condition, however, in which hyperglycemia also occurs.

A slight increase in the sugar concentration of both the blood and spinal fluid occurs in some cases of epilepsy, as it does in certain other nervous conditions, but the variety of cases observed in this series of 33 cases, and consequently the limited number of any one disease, renders inadequate any conclusion drawn at this time.

Syphilis frequently reveals lower figures than any other condition, with the exception of meningitis.

The micromethod for estimating the reducing substance of the spinal fluid has proved to be of value owing to its simplicity, reliability, and the small amount of fluid required.

Fehling's test is unreliable and misleading unless the proper dilutions are constantly used together with equal parts of the fluid and the solution. In the latter case fairly constant relative results are derived when there is a marked change in the amount of glucose and when there is not an excess of protein. Quantitative estimations of the glucose concentration of the spinal fluid are of distinct value from the standpoint of very early diagnosis and prognosis, especially in meningitis.

It remains for further investigations to reveal the value of this test in nervous disorders and syphilis.

I wish to express my thanks to the physicians and members of the resident staff of the University, Pennsylvania, Polyclinic, and Children's Hospitals, and especially to Dr. Rosenberger and Miss McNitt, of the Philadelphia General Hospital, for the contribution of the fluids examined.

TUBERCLE BACILLI NOT STAINABLE BY ZIEHL: THEIR CLINICAL SIGNIFICANCE.[1]

By Charles N. Meader, M.D.,
DENVER, COLORADO.

In 1907 Hans Much published his original paper "Upon Gram-positive Forms of the Tubercle Bacillus, Not Demonstrable By Ziehl." Since that date his work and conclusions have been substantiated and confirmed by many other investigators. The importance of these findings, however, seems to have been appreciated chiefly abroad, and no such interest as they deserve has been aroused in this country. It has therefore seemed worth while to report upon a small series of cases studied by a modification of his method, with a brief review of the more important literature of the subject.

It is generally known and regretted that a considerable number of clinically suspicious or positive cases of tuberculosis of various organs cannot be bacteriologically proved, even after careful concentration of material and painstaking search for bacilli; it has also been recognized that in a certain number of such cases this material can infect the guinea-pig. Starting with the assumption, already considered by von Behring and others, that this discrepancy arises from the existence of a form of tubercle bacillus which does not take the Ziehl stain, Much[2] was able to demonstrate certain granules by the use of a modified Gram stain. These were small, round, blue-black bodies of varying size, sometimes showing a reddish tinge, sometimes isolated, frequently arranged in rows of from two to eight granules. These forms were found in the tubercles of a guinea-pig which had been injected with a culture of bovine tubercle bacilli, Ziehl organisms being undemonstrable. They were also present in the Ziehl-negative lung of a tuberculous calf. Pieces of this lung were incubated on serum tubes; after the third day the number of granules rapidly increased, and on the sixth day Ziehl-staining forms appeared. These results were confirmed on other animals. The pus from two cold abscesses was found to contain no Ziehl-staining organisms after prolonged search, but did contain numerous Gram-staining forms, and upon inoculation into guinea-pigs, produced typical tuberculosis, showing many Ziehl-positive bacilli. Much concluded that there is a form of tubercle bacillus not staining by Ziehl; that this form is a virulent but degenerated type, and that its staining properties are dependent upon different constituents than those which take the Ziehl stain.

[1] This article was received for publication April 15, 1915.
[2] Beitr. z. klin. d. Tuberk., 1907, viii, 85.

These results and conclusions have been confirmed and extended by Much himself and by many others down to the present time. In 1908 Wirths[3] confirmed Much's original work in detail upon cases of human glandular tuberculosis and cold abscesses in which the Ziehl stain proved negative, the Gram stain positive, and the material infective to guinea-pigs. In these guinea-pigs he showed that the peritoneal exudate at first contained grandular forms, that these rapidly gave place to small Gram-staining bacilli, and these in turn to Ziehl-positive forms. Adding the pus from cold abscesses plus a culture of human bacilli to milk, he found that the Ziehl forms rapidly diminished or disappeared with a replacement by Gram-staining forms, and further noted that after a few days the Ziehl forms began to reappear. His conclusions entirely substantiated those of Much, and he considered a transition from one form to the other proved.

It is not necessary to note all the numerous reports scattered through the literature which confirm the general proposition that tubercle bacilli may be demonstrated by the modified Gram method in material in which no trace of them can be found by that of Ziehl. Certain of these reports, however, are of special interest as helping to clear up disputed points of etiology and diagnosis. In the field of dermatology, Lier[4] has found Gram forms present, and Ziehl forms absent in a small series of tuberculids and in lupus vulgaris. In 13 cases of the latter disease, Krüger[5] found only three positive by Ziehl, while Much forms were present in the lesions of all. Boas and Ditlevsen[6] among 20 such cases found Gram-staining forms in all, though only four were positive by the Ziehl stain. It is interesting to note in passing that the morphologically similar bacillus of leprosy also shows granular forms staining only by Gram, and that these have been found present where Ziehl-staining organisms failed.[7]

Weiss,[8] among eight cases of tuberculosis of the cervical, bronchial, and mesenteric glands, clinically and pathologically proved, was able to find no Ziehl-staining bacilli, though Much forms were present in all. The mesenteric lymph nodes of twenty-one children were examined by Wolff,[9] of which cases six were clinically and pathologically tuberculous. Of these six the lymph nodes in four were positive by Ziehl, in all by Gram. Of the remaining fifteen in whose glands there was neither macroscopically nor microscopically any suspicion of tuberculosis, Gram-staining Much organisms were found in three, in one of which, guinea-pig inoculation proved positive with the recovery of Ziehl-staining bacilli. This

[3] Münch. med. Wchnschr., 1908, lv, 1687.
[4] Centralbl. f. Bakteriol., Orig., 1909, li, 678.
[5] Münch. med. Wchnschr., 1910, lvii, 1165.
[6] Berl. klin. Wchnschr., 1910, xlvii, 2106.
[7] Arning and Lewandowsky, Deutsch. med. Wchnschr., 1909, xxxv, 1225.
[8] Münch. med. Wchnschr., 1909, lvi, 443.
[9] Ibid., lvi,2312.

report is of special interest in view of the well-known periods of latency of tuberculosis.

Schottmüller and others[10] have reported the finding of Gram forms in the urine in tuberculosis of the urinary tract, although Ziehl forms were few or failed altogether. In the field of dentistry, Zilz[11] has contributed an interesting piece of work, finding and proving by guinea-pig inoculation the presence of granular forms of the tubercle bacillus in carious teeth. This is again of importance for the question of latent infections. In the field of ophthalmology, Wehrli[12] has found the granular forms of the bacillus in nodular keratitis, thereby confirming the previously suspected tuberculous nature of this lesion. The much disputed question of the frequency with which tubercle bacilli are found in the circulating blood has been studied from this new view-point. Jessen and Rabinowitsch[13] found in the blood of thirty-six patients the Gram-staining form nine times, the Ziehl seven. Sturm[14] in a series of pulmonary cases found the blood in 22 per cent. positive by Ziehl, in 42 per cent. by Gram, and in 46 per cent. positive by guinea-pig inoculation.

Fraenkel and Much[15] developed that phase of the subject which has aroused most widespread attention when, in 1910, they reported that there are present in the glands of Hodgkin's disease and of lymphatic leukemia structures which cannot be distinguished morphologically from those described by Much in tuberculosis. These observations have since been confirmed by other investigators and the organisms found further studied. Their exact relationship to the tubercle bacillus, whether an attenuated and culturally different type of it or whether only a more or less closely related organism, is not yet clear.

The relation of granular forms of the virus to pulmonary tuberculosis has, of course, not failed of investigation. Körber[16] examined the sputum in 167 cases of suspected pulmonary tuberculosis and found Ziehl-staining organisms in 54 per cent., Gram-staining forms in 64 per cent. Weirauch[17] reports the examination of fifty sputa of which 16 per cent. were positive by Ziehl in direct smears, 52 per cent. by Ziehl after antiformin concentration, and 72 per cent. positive by Much's modified Gram method. The antiformin treated sediment of one of these sputa, negative by Ziehl but positive by Gram, was injected into a guinea-pig which died forty-eight hours later of a thrombus. In this thrombus were found

[10] Münch. med. Wchnschr., 1908, lv, 2564; Leschke, Centralbl. f. Bakteriol., Orig., 1911, lix, 365.
[11] Beitr. z. klin. d. Tuberk., 1912, xxii, 97.
[12] Klin. Monatsbl. f. Augenh., September, 1909.
[13] Deutsch. med. Wchnschr., 1910, xxxvi, 1116.
[14] Beitr. z. Klin. d. Tuberk., 1911, xxi, 239.
[15] Münch. med. Wchnschr., 1910, lvii, 685.
[16] Deutsch. med. Wchnschr., 1912, xxxviii, 1494.
[17] Ztschr. f. Tuberk., 1909, xiv, 511.

many short Ziehl-positive bacilli. Böhm[18] found among twelve Ziehl-negative sputa nine positive by the modified Gram method. Teleman[19] reported the presence of Gram forms in ten cases of lung tuberculosis, all of which were negative by Ziehl but positive on guinea-pig inoculation. An important piece of work is that contributed by Neumann and Matson,[20] who examined the sputum in forty-two cases of chronic lung disease. All were of long duration, with relapses, continued cough with considerable sputum; several were clinically "old-age emphysema," all were resistant to test tuberculin, but would clinically arouse suspicion of tuberculosis. In two of four tests the sputum proved infectious to guinea-pigs. Of this series all were negative by Ziehl; fourteen showed Much forms.

While the great majority of reports substantially uphold Much's early conclusions as to the value of the method, opposition has not been wanting. It was early objected, with justice, that the presence of cocci in sputum and in other pathological specimens introduced a grave source of error through the readiness with which they might be confused with the somewhat similar granules. With the use of antiformin, by which all non-fast bacteria are dissolved while the resistant granules remain intact, this argument has entirely lost its force. A second objection is found in the papers of a series of men who sought to show that the Gram stain demonstrates no more bacilli than does the Ziehl. This objection, as Much justly observes, entirely misses the point of the matter, for the value of his method lies not in the relative number of bacilli shown in a given specimen, but in the fact that the Gram stain not infrequently shows the presence of the granular forms in specimens in which no Ziehl forms at all are to be found. The most determined opposition has arisen from Spengler and his school, who do not deny that there is a form of tubercle bacillus not demonstrable by Ziehl, but insist that Much's granular forms and Spengler's "splitters" are identical, that Much has simply stained these structures in a new way and deserves no credit for their demonstration. The discussion need not be entered upon here, being largely theoretical, chiefly turned upon the question of priority and somewhat embittered; it is sufficient to say that the balance of evidence supports the view that granules and "splitters" are not identical and that Much deserves all credit for his discovery.

The biological relationship of Much forms to Ziehl-staining forms of the tubercle bacillus is a matter of considerable interest. They may be considered as a natural stage in the evolution of the bacillus, as the result of degenerative changes, or may be classed as spores (*i. e.*, as resisting forms). The evidence which has accumulated tends

[18] Centralbl. f. Bakteriol., Orig., 1911, lxii, 497.
[19] Deutsch. med. Wchnschr., 1910, xxxvi, 891.
[20] Beitr. z. Klin. d. Tuberk., 1912, xxiv, 193.

to show that they are predominantly found in tissues of a distinctly fibroid character, in old cavities, in the pus of cold abscesses, in old cultures, in the notably indolent lupus lesions, and in sclerosed lymph glands—facts which, taken together, mark them as forms assumed under unfavorable conditions, whether they be the result of sporulation or of degeneration. The same conclusion is suggested by observations that under favorable cultural conditions they are rapidly replaced by Ziehl-staining forms. In this connection the work of Wirths noted above is of interest. His experiment is further supported by one of Much's, who incubated pus from a renal abscess, in which microscopically only granular forms could be seen, in Heyden bouillon, and after five days found Ziehl-positive bacilli in pure culture. He further added a Ziehl-positive culture of bovine bacilli to the perhydrase treated milk of a tuberculous cow and found that the Ziehl forms gradually diminished and disappeared. When glycerin was added to a portion of this culture, Ziehl-positive forms promptly reappeared.[21] Against their classification as spores in the commonly accepted sense is the fact that the granular forms are rather less resistant to the action of antiformin than are the Ziehl forms; their resistance to other chemical and physical agents has not yet been reported upon. It is of interest to note here that the granular forms appear more frequently in the bovine than in the human type of bacillus.

Closely allied to the problem of their biological relationship is that of the chemical relation between Ziehl and Much forms. Here the views of Deycke and Much are probably correct. Starting with the fact that the Ziehl-staining property is dependent upon the fatty acid component of the bacillus, they believe that a progressive loss of this substance coincides with a progressive diminution in the intensity and uniformity of the Ziehl stain; with its complete loss the bacillus no longer stains at all by Ziehl. There remains, however, a substance capable of taking the Gram stain, probably a proteid. This material is impregnated with the neutral fat component which serves to protect it in some degree against the stain, accounting not only for the slowness with which this acts, but also for the fact that Much forms, unlike other bacteria of protein composition, are antiformin-fast. In support of this view, Deycke and Much[22] planned experiments with the action of neurin and other solvents upon masses of tubercle bacilli, and found that by increasing the action time of such solvents the Ziehl stain could be made to become progressively weaker, Gram forms replacing Ziehl forms. These were in turn replaced by a homogeneous mass, at first staining by Gram, later failing to take any stain. According to this view the loss of fatty acid is a degenerative change, brought

[21] H. Much, Berl. klin. Wchnschr., 1908, xlv, 691.
[22] Münch. med. Wchnschr., 1909, lvi, 1985; ibid., 1910, lvii, 633.

about by the protective forces of the body, or, as in the centre of caseous lesions, by a possible deficiency in nutriment. Matson has suggested that the fat-splitting ferments of the lymphocytes play a prominent part in the removal of fatty acid and that the proteolytic ferments of the leukocytes are very possibly responsible for the final degeneration of the granules themselves.

The investigations to be here reported comprise forty-six sputum examinations upon forty-four patients, in all of whom lesions of the lung or of the bronchial or mediastinal glands were clinically present or suspected, but whose sputum on direct examination contained no tubercle bacilli. Many known positive sputa were also examined by this method; all contained many Gram-staining as well as Ziehl-staining forms. Where possible, two or three ounces of sputum has been used, otherwise the entire twenty-four expectoration. A direct smear was in all cases first examined by the usual Ziehl-Nielsen stain. The sputum was then concentrated by the modified Ellerman-Erlandsen method as follows: an equal amount of 0.6 per cent. sodium carbonate was added, the whole thoroughly shaken and allowed to stand at 37° C. for twenty-four hours; if complete homogenization had not occurred the time was extended to forty-eight hours. This mixture was then centrifuged five minutes at high speed and to the sediment an equal amount of 30 per cent. antiformin added. Digestion was allowed to proceed for twenty minutes, the mixture again centrifuged, the sediment washed with water to remove excess of antiformin, again centrifuged, and smears made from the resulting sediment. In searching for Much forms the so-called "double stain" of Weiss was used. This consists of three parts of ordinary carbol fuchsin solution to one part of a carbol methyl violet solution, the latter prepared by adding nine parts of 2 per cent. carbolic water to one part of a saturated alcoholic solution of methyl violet. This stain is useful for about two weeks if not exposed to the air or to direct sunlight; after this time a precipitate forms rendering it useless.

The technique found to give the most satisfactory results is as follows: the smear is immersed in the stain for forty-eight hours at room temperature, washed gently, covered with Gram's iodin solution for five minutes, being brought to gentle steaming, decolorized with 5 per cent. nitric acid for one minute, 3 per cent. hydrochloric for ten seconds, and washed with a solution of equal parts of acetone and 95 per cent. alcohol until no more color is removed. After drying the smear is ready for examination. No counterstain was used, as it was found that this added nothing to the ease of search and could at times prove confusing. Many modifications of this method were tried, including a quick method, in which steaming replaced the forty-eight-hour exposure to the stain, the use of a twenty-four-hour exposure, the effect of longer staining in the cold, and the relative value of I. K. I. and Lugol's solution as a

mordant. The above outlined method was found to give the most clear-cut and reliable preparations, and all results were based upon it. In addition to a direct smear, a smear of the concentrated sputum was in each case examined by the Ziehl stain to serve as a control for the presence of Ziehl-staining bacilli in the antiformin concentrated sputum, and for the presence of undigested cocci which might prove a source of confusion with the Much granules. In several instances cocci were thus recognizable, and such preparations are omitted from consideration. Twenty minutes' search of a good preparation, using a mechanical stage, has been taken as a standard before either direct smears, concentrated sputum, or Much-Weiss preparations have been recorded as negative.

With this method the granules appear as small, round, sometimes slightly ovoid bodies, frequently refractile, varying somewhat in size from a half to three-quarters the size of a staphylococcus, *i. e.*, about 0.4 to 0.5 microns in diameter. In color they are of a blue- or violet-black, with sometimes a faint tinge of red. They may occur singly, sometimes in small groups, but are more often arranged in chains of from two to eight granules, usually of not more than four. The granules thus arranged in chains usually, but not always, show a faintly bluish tinged substance connecting them; this bacillus body may have a faint or a marked red tinge. In other instances isolated granules may show a delicate red halo or a faintly reddish prolongation. These various figures may all be found in known Ziehl-positive sputa, and the intermediate forms from the small isolated granule on the one hand to the solidly red bacillus on the other may be readily traced. Having regard to the somewhat remote possibility of confusion with cocci, only those preparations have been recorded as positive in which the granules either appeared in characteristic chains with a connecting substance between or showed a definite reddish prolongation.

The cases studied group themselves clinically into three rather distinct classes. First are those in which the tubercle bacillus has at some time been demonstrated, but has since disappeared coincidently with clinical healing. Of these some have at the time of examination complained of symptoms suggesting a recrudescence of the old process; others have been subjectively and clinically well, save for slight occasional expectoration. In this group are comprised nine patients in whom the results were as follows:

	Positive.	Negative.	Per cent. Positive.
Ziehl (direct smear)	0	9	0
Ziehl (concentrated sediment) . . .	1	8	11
Much-Weiss method	6	3	66

A second group comprises those cases in which signs and symptoms warrant the suspicion of an early or of a mild, longer continued

tuberculous process in lung or mediastinum, but which have shown a persistently negative sputum. Fifteen cases are included in this group, among whom the results were as follows:

	Positive.	Negative.	Per cent. Positive.
Ziehl (direct smear)	0	15	0
Ziehl (concentrated sediment)	2	13	13
Much-Weiss method	11	4	73

The largest and most important group comprises those cases in which the clinical picture is that of long-standing cough with more or less profuse expectoration, subject to exacerbations and remissions, occasional manifestations of a mild toxic absorption, and upon physical examination, signs, sometimes of a fibroid process of varying extent, sometimes of bronchiectasis, sometimes of chronic bronchitis or emphysema. Occasionally there are signs suggesting glandular enlargement in the mediastinum or root of the lung with an otherwise negative chest. Here too are included several cases of recurring asthmatic attacks without other symptoms. A few of this group are reported to have shown tubercle bacilli at one time or another, some have undergone sputum examinations extending over many years with no positive result. Among this group the results are as follows in twenty-two examinations:

	Positive.	Negative.	Per cent. Positive.
Ziehl (direct smear)	0	22	0
Ziehl (concentrated sediment)	2	20	9
Much-Weiss method	18	4	82

In addition, one specimen of chest fluid from a patient with frank lung tuberculosis has been found to contain Gram-staining forms though no Ziehl-staining organisms could be demonstrated. Also, the urine from a patient with clinically undoubted tuberculosis of the bladder contained rather numerous Gram forms, though the Ziehl stain gave entirely negative results.

If the results in these three groups be added together, it will be found that of the 46 examinations 5, or a little over 10 per cent., were positive for Ziehl-staining organisms in the antiformin concentrated sputum, while 35, or about 76 per cent., showed Gram-staining forms. The preponderance of sputa containing Much forms in Groups II and III seems especially significant upon the supposition that this type represents a resistance form of low virulence. The individuals of the latter group were nearly all leading rather active normal lives, and were not seriously inconvenienced by the cough, slight shortness of breath, recurrent asthmatic attacks, frequent attacks of acute bronchitis, or mild toxic symptoms for which they presented themselves. The results in this group are further of considerable significance for the prophylaxis and prevention of

tuberculosis. The readiness and rapidity with which these granular, Gram-staining forms may, under favorable conditions, transform themselves into virulent Ziehl-staining bacilli has been proved by the work of Much, Wirths, and others as noted above. If now these forms are present in the background of some proportion of cases of chronic bronchitis, old age emphysema, recurring asthmatic attacks, and other chronic lung conditions in which there seems no reason for suspecting tuberculosis, and so for enforcing proper care of the sputum, it is not hard to believe that such cases may be a really important factor in the spread of tuberculosis.

The individuals in these groups represent common types of patients in whom the problems of diagnosis or of management may be puzzling. In the first group this uncertainty presents itself in the necessity of deciding whether a slight occasional expectoration or a tendency to frequent colds with accompanying expectoration, in the presence of otherwise entirely negative findings, is to be regarded as significant of continued active infection. In the second group there arises the question whether trifling or obscure symptoms and physical signs have anything to do with tuberculosis; upon a correct decision depend most important questions of management. The widely varying clinical pictures of the third group may suggest equally various possible etiologies, of which a latent tuberculosis may appear the least probable.

In conclusion, it may be said that this work, undertaken with some skepticism, has resulted in the conviction that the granular forms described must be regarded as identical, for diagnostic purposes, with the ordinary Ziehl-staining form. In any patient suspected of tuberculosis in whom Ziehl forms cannot be demonstrated, it is as important to search for Gram-staining forms as it was for the Ziehl-staining bacilli, and a diagnosis of tuberculosis cannot be certainly excluded until such search has proved negative. The type of case in which they are characteristically present strongly supports the conception that they represent a resistance stage of low virulence, and their presence alone warrants a much more favorable prognosis than does the presence of Ziehl forms. Further, they are probably a definite factor, of as yet undetermined importance, in the spread of tuberculosis.

I wish to thank cordially Doctor Carroll E. Edson for the privilege of studying many of these cases and for much kind assistance in the work.

The following histories of patients showing Much forms are appended as typical of those cases which have been grouped in each of the three classes above noted.

Group I. H. B., a single man, aged twenty-three years, has had since he was twelve years old two or three asthmatic attacks a year, coming usually in winter, lasting three or four weeks. There have been no attacks for the past three years, but he has had

several severe colds each winter. In the spring of 1912 he began to "run down," was tired, with not much loss of weight. Cough began in July with a little yellow expectoration. Tubercle bacilli were found in September, 1912. At this time he had dulness, increased fremitus and whisper, prolonged breathing, and a few rales after cough at both apices in front. No fever.

Under rest for four months the cough and expectoration entirely ceased, the rales disappeared, and in six months he took up active business. In September, 1913, he took a three days' trip, involving laborious mountain climbing, without apparent ill effect.

During January and February, 1914, he had a succession of severe colds, with temperature, cough, sweating, and much loose expectoration. When seen in April he had occasional cough, with slight white expectoration. No signs of activity could be detected in the lungs; he was afebrile and his general condition was excellent. At this time the sputum was negative to Ziehl, both in direct smear and in the concentrated sputum, but positive by the Much-Weiss method, showing many scattered granules and occasional chains of two or three. Both cough and sputum have since entirely disappeared.

Group II. Mrs. J. F., aged thirty-two years, had, in September, 1912, a bronchopneumonia in the left lower lobe, and was in bed five weeks. This was followed by a dry pleurisy on the right side. Since then there has been a persistent cough, with a little morning expectoration (January, 1914). She has had several mild attacks of bronchitis this winter with increased cough and expectoration. There has been one negative sputum examination. She was at this time twenty-five pounds below weight, very nervous; the pulse was 100 to 110, with no elevation of temperature. There was occasional pain under the sternum without relation to food or exertion, and no other symptoms.

Chest examination showed slight dulness in the right mid-back from the fourth to the eighth rib inside the scapula, without change in voice or respiration. No rales. The chest was otherwise entirely negative. The Roentgen-ray gave a definitely enlarged bronchial gland shadow corresponding to the area of dulness. Sputum examination was negative for Ziehl-staining forms in both direct smears and concentrated sediment. By the Much-Weiss method there were present chains of two and three granules, and occasional granules showing definite reddish prolongations.

Under rest and forced feeding the patient has gained weight and is less nervous; the substernal distress has disappeared, cough and sputum have gone, and she feels well. The chest examination remains the same.

Group III. C. R. R., a widower, aged forty years. One brother died of tuberculosis ten years ago. The patient had pneumonia twenty years ago. In 1907 he had an acute appendicitis, with

operation, and has never regained his full strength. Sometime during that year he began to have considerable cough and expectoration, which has continued since. In December, 1909, he was in bed for a month with a "heavy cold," having much cough, fever, and sweats. In the spring of 1910 he had blood in the sputum, with a great deal of pleural pain in the right lower axilla. Sputum examination was negative for tubercle bacilli. The chest in January, 1911, showed exaggerated breathing at the right apex, with feeble breathing and a few moist rales in the right lower axilla.

From this time until seen in January, 1914, he has had continuous cough, with from a quarter to two ounces of yellow sputum a day; occasionally this has been blood-stained. He has had numerous acute flare-ups with fever, lasting one to three weeks, and has complained at various times of considerable muscular and joint aching. The chest has repeatedly shown rales at one or both apices, above and below the clavicles, and in the right lower axilla, but on the whole there has been little permanent extension of involvement. Repeated sputum examinations have been negative for tubercle bacilli. He has continued an active business life.

Sputum examination in January, 1914, showed no Ziehl-staining organisms either in direct smears or in concentrated sediment. In the Much preparations there were present very many granules, arranged both in short chains of two and three and in long chains of four, five, and six granules.

Since this time his general condition and symptoms have remained much the same. A further sputum examination has not been possible.

HODGKIN'S DISEASE: A STUDY OF A SERIES OF TWENTY-FIVE CASES.

By W. F. Cunningham, M.D.,
SENIOR INTERNE PATHOLOGIST, ROOSEVELT HOSPITAL, NEW YORK.

(From the Pathological Laboratory of The Roosevelt Hospital.)

In the past five years we have had at the hospital 23 cases of Hodgkin's disease; 6 were females and 17 males; of the latter 1 was a negro. This gives a ratio of 1 female to 2.8 males, but the admission proportion to this hospital is 1 female to 1.7 males. Considering this from our experience, it is relatively and absolutely more common in men than in women. Reed's[1] series gave 7 males to 1 female, and Bunting,[2] in two series, gives 15

[1] Johns Hopkins Hosp. Report, 1902.
[2] Johns Hopkins Hosp. Bull., 1914, xxv, 173.

to 10 and 15 to 13. Clark[3] refers to a series of 43, 37 of which were in men, and Ziegler, 149 males and 71 females. Roughly this shows it to be about twice as common in men as in women.

Thirteen of the cases occurred in the third and fourth decades, and four each in the first and second. We are unable to make the distinction referred to by Bunting of the majority of males being under 34 and that of females being over 33. It is generally accepted as a disease of youth and early adult life, with occasional cases at both extremes. Ziegler gives 45 per cent. of cases between 21 and 40.

The primary foci have been, as far as observation permits, cervical 13 (left 7, right 4, undetermined 2), axillary 3, retroperitoneal 3, right femoral 1, intestinal 1, and undetermined 2. Of the latter the first lesion noted was the skin, but we do not consider this as primary. Practically all writers agree to a primary cervical involvement in the majority of cases, and suggest the mouth, gums, tonsils, nose, and accessory sinuses as the portal of entry of the infecting agent. Reed[4] considered all cases of this origin, saying that no case had been described in sufficient detail to permit of a positive statement that the disease started elsewhere. We have had one case of primary intestinal origin, and Bunting[5] details a case of inguinal involvement following a cystitis. Three of the cases were diagnosed following operation and removal of retroperitoneal tissue. These cases are, in all probability, of primary intestinal origin. In only two of our cases (5 and 16) has the onset been definitely traced to previous infections, and both of these were from the throat, tonsillitis, and diphtheria.

The following cases are cited from Ziegler's[6] series of 220 cases. Primary cervical involvement 50 per cent., supraclavicular and submaxillary 6 per cent., axillary 10 per cent., mediastinal and inguinal 3 per cent., spleen 9 per cent., and retroperitoneal 10 per cent.

It is found more commonly in the lower classes, but that it is quite cosmopolitan in its tendencies is shown by the fact that eight countries are representated in this short series.

The time elapsed between the first sign of the disease and consultation has varied from a few weeks to ten years, with an average of ten months. The following are given as the reasons for consultation:

1. Tumor alone, 14.
2. Pain alone, 4 (epigastric, 1; right, lower abdomen, 2; right arm, 1).
3. Tumor and pain, 2.
4. Chills and fever, 2.
5. General weakness, 1.

[3] British Med. Jour., 1901, ii, 701.
[4] Loc. cit.
[5] Loc. cit.
[6] Die Hodgkinische Krankheit, Jena, 1911.

Eight of the cases were without symptoms throughout the observed course, but all of these with one exception were under six months' duration; of the remaining 15 cases, 5 complained of pressure pain, 4 abdominal pain, obstruction, gastric ulcer, and appendicitis, and 2 of general body pain. It is to be regretted that we did not have autopsies in more cases, but particularly in Case 20, who suffered severe pain in the back and bones, to determine a possible relation to myeloma or myeloblastic pseudoleukemia of Sternberg.[7]

The other prominent subjective symptoms were general weakness and chills and fever in 6 cases, loss of weight in 8, profuse night sweats in 4, pallor in 2, pruritus in 2, toxic vomiting and jaundice each 1. One writer[8] refers to prurigo exantheme as a frequent early symptom, in one case having been present for three years before the development of glands. In only two of the cases did such symptoms appear before one year, and in one of the cases chills, fever, and sweats were the first symptoms; Cases 14 and 15 developed such two months after onset.[9] Both these cases left the hospital against advice in very poor condition, the former with a temperature of 105°, the latter 103°, and lived only a short time. In the other cases such symptoms developed after one year. We consider from a clinical stand-point two types, symptomatic and latent.

SYMPTOMATIC TYPE. (*a*) acute, 3 cases; (*b*) chronic, 18 cases.

(*a*) Symptomatic Hodgkin's disease, as will be seen from the analysis, might be classified as acute and chronic. The former gives a distinct picture of acute toxemia, simulating typhoid, sepsis, or malaria, and runs its course in a few weeks to six to eight months, with progressive loss of weight, general weakness, chills and fever, night sweats, and sometimes vomiting. We have had three cases of this type, 10, 14, 15. Osler[10] believed that such reactions were probably due to an intercurrent infection.

Such cases are those reported by Karsner,[11] Chark,[12] Hirschfield, and Isaac.[13] In the latter cases a description of one of the glands suggests that it was probably longer than six weeks' duration, and of the type described in the next group. As the course of this case was so acute, I will detail a brief *résumé*. The patient, age sixty-one years, gave a history of swelling of the back of neck, of four weeks' duration, followed shortly by marked weakness, swelling of feet, and difficulty in breathing. The left cervical, right supraclavicular, and both axillary groups were moderately enlarged. The temperature was 101.4° to 103.6° F.

[7] Verhandl. d. deutsch. path. Gesellsch., 1912.
[8] Pathologie d. primarer Krankungen des Lymphatischen and hematopötischen Apparates, 1915.
[9] Ziegler, Loc. cit.
[10] Practice of Medicine, New York, 1907.
[11] Arch. Int. Med., 1910, iv, 175.
[12] British Med. Jour. 1901, No. 2, p. 701.
[13] Med. Klinik., 1907, lii, No. 52.

The blood findings changed in two weeks from Hb. 20 per cent., red blood cells 2,290,000, white blood cells 24,000, to Hb. 15 per cent., red blood cells 1,190,000, white blood cells 20,000. In six weeks from the onset of the swelling the patient died, running a subnormal temperature for several days before death. Ziegler[14] cites a case of a few weeks' duration, and one very suspicious case acutely toxic of but a few days' duration.

(*b*) By the chronic cases we refer to those of long duration, characterized by exacerbation and remissions. These cases we find to be of more than a year's duration, and many under better hygienic conditions, excision of active foci, hospital routine, and Roentgen-rays improve remarkably for certain periods, but the time comes when all these measures fail. The subjects pass into a state which characterizes the acute cases, the picture of acute toxemia develops with high intermittent fever, which becomes subnormal a few days before death.

Case 6 appears as a good illustration of the effects of energetic Roentgen-ray treatment, the exacerbations and remissions clinically and subjectively, but with progressive lymphatic enlargement. All but five of the cases appear as this type.

LATENT TYPE. Two cases.

The latent type manifests itself in a prolonged course over a period of years, with little if any subjective symptoms, save those referable to the local disturbance, absence of fever, chills and sweats, but characterized by pathological exacerbations in that the glands alternately increase and decrease in size. As an example *par excellence* of this variety we offer Case 24, of twenty-five years' duration. Nowhere in the literature have I been able to find a case which approaches this in duration; the longest was a case of seventeen years. This man, with the exception of the disfiguration, appears in perfect health. A second case, 23, stands as another example. Of these cases the latter gives a typical pathological picture, but the picture of the former is masked by fibrosis. This type of case is of rare occurrence; by far the larger majority of cases come under the heading chronic symptomatic; that is, the type of case which, according to Reed, Bunting, and others, runs its course in from three to five years.

Many writers have attempted to designate Hodgkin's disease from the tissue or location in which it develops, calling it abdominal, splenic, hepatic, or lymphatic; but this classification is to be discouraged, as it is a systemic disorder, with marked local manifestations. Sternberg[15] advises the term pseudoleukemia for the groups lymphosarcoma, lymphogranuloma, and plasmoma, diseases with hyperplasia of lymphoid without leukemic blood findings, and speaks of an analogous disease of myeloid tissues,

[14] Loc. cit.

[15] Verhandl. d. deutsch. path. Gesellsch., 1912, p. 22; ibid.

"myelogenous pseudoleukemia." In contrast to this teaching, however, are the cases of Symmers[16] and Ziegler[17] of solitary splenic involvement.

The spleen was involved in seven of the cases, the liver in four, and the lungs and kidney in the case with autopsy. At the present time one of the patients has a diffuse infiltration of the left breast and a few nodules in the right. The above figures are certainly low, for the majority of the cases were seen in the first year. Could we have seen them at later dates our figures might nearer approach Clark's[18] as in half of his cases an enlarged spleen was noted, while Ziegler gives 65 to 75 per cent. of cases with splenomegaly. The involvement of internal organs is merely a question of time, and though a disease primarily selectively lymphatic, it causes a

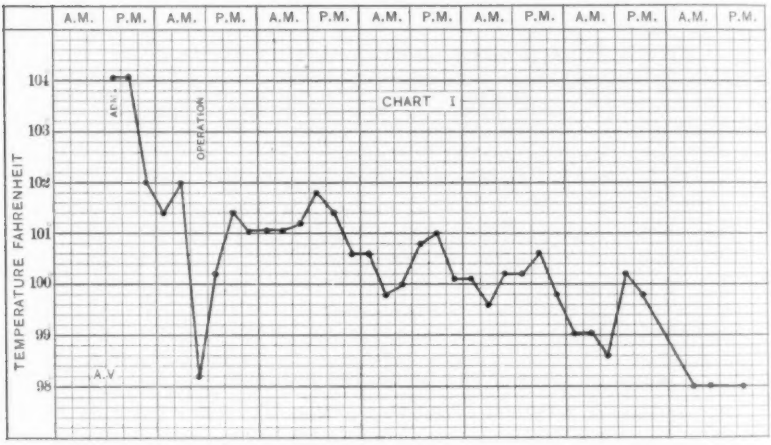


CHART I

compensatory lymphogenesis in other organs with subsequent involvement. It is on account of this fact that Hodgkin's disease has been considered in the light of a new growth, but for late years there has been a tendency toward the opinion that it is of an inflammatory nature, occasionally showing malignant transformation. Tusnoda[19] is of the opinion that it is primarily a malignant tumor of lymphoid elements, with the inflammation as a matter of secondary importance. Dietrich[20] believes it to be a granulomatous lymphosarcoma. Symmers,[21] Harsner,[22] Yamasaki,[23] and

[16] Arch. Int. Med., 1909, iv, 218.
[17] Loc. cit.
[18] Loc. cit.
[19] Virchows Archiv, Band cciv, 265.
[20] Deutsch. med. Wchnschr., 1908, Heft. 27.
[21] Loc. cit.
[22] Loc. cit.
[23] Ztschr. f. Heilk. 1904, xxv, 269.

and Hirschfield,[24] are of the opinion that it is primarily Hodgkin's, but may undergo malignant transformation.

The Wassermann reaction was made in seven cases and was found negative in each instance.

TEMPERATURE. In thirteen of the cases the temperature was normal during observed course. It does not seem to be entirely dependent upon the duration of disease and the extent of involvement, but upon some factor which at present we are unable to reckon with. The duration varied in afebrile cases from two months to twenty-five years, but the larger percentage averaged about six months. This coincides with the absence of other clinical symptoms which, as we have seen, occur in the majority of cases after six months. The extent of involvement in these non-febrile cases was as follows: unilateral cervical 5, general glandular 2, retroperitoneal 2, femoral 1, and general glandular with enlargement of liver and spleen 1.

The cases we have had an opportunity to observe for much longer periods are those clinically ill with all the signs of an acute infection with a very variable temperature. Here the duration is seen to be of more than seven months in the majority of the cases. The known involvement in these cases was bilateral axillary and cervical 2, bilateral cervical 1, retroperitoneal 2, general glandular 1, cervical and spleen 1, and extensive glandular and visceral 1. Considering these cases individually, many similar cases will be found in the foregoing group. This fact is certainly a strengthening link in the infectious theory.

From a study of the temperature charts of these cases the striking feature is the extreme irregularity of the temperature wave. There is no set type for any one case, for all the classical curves, of tuberculosis, typhoid, sepsis, and malaria, are simulated, the tuberculous type perhaps being more often seen. No two charts resemble one another. One case, Chart I, with early retroperitoneal involvement, was admitted to hospital with a temperature of 104° and a suspicious history of acute appendicitis. At operation the appendix was found to be normal but about the cecum was a rather extensive glandular enlargement, a small portion of which was excised for diagnosis. The temperature gradually descended to normal on the sixth day, and remained so.

Another case, Chart II, with a history of several months of attacks of fever, chills, and sweats, was admitted to hospital, and for nine days temperature was normal. It then rose in twenty-four hours to 102.6°, with a morning drop to 99° to 103.6° and 104° on the two following days. For six days it again remained normal, with gradual rise to 104°, oscillating between 101° and 105° for five days, and continuous 104° to 105° for three days, when the patient left the hospital against advice and has not been heard from

[24] Folia Hemat., 1910, x, 67.

since. This is the best example we have had of the so-called Pel Ebstein recurring fever. This type of fever, according to Fabian,[25] occurs in about 50 per cent. of cases, and is seen in other conditions, such as carcinoma of internal organs. The same writer quotes Gowers, finding it in two-thirds of cases. According to Zeigler it occurred but eight times in a series of 220 cases.

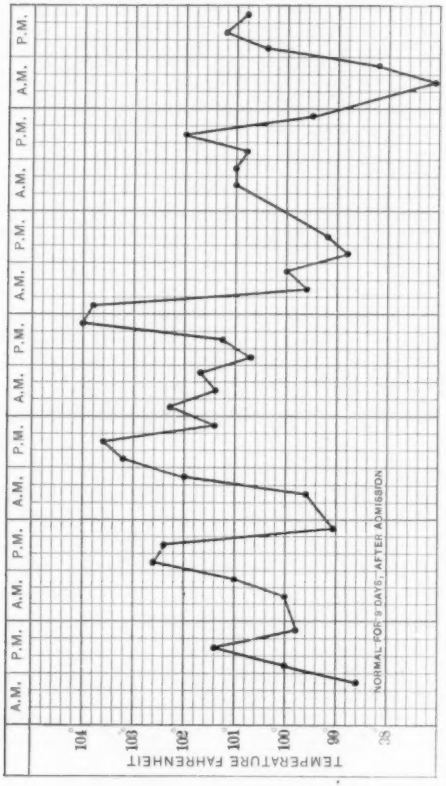


CHART II

Chart III is that of a boy, aged nine years, who a year previous, with extensive cervical involvement, had a normal temperature through six weeks' observation. The reaction as seen in the chart was followed for nine weeks by practically a normal temperature. One year later temperature for eleven weeks was very irregular,

[25] Centralbl. f. Allg. Path., 1911, xxii, 145.

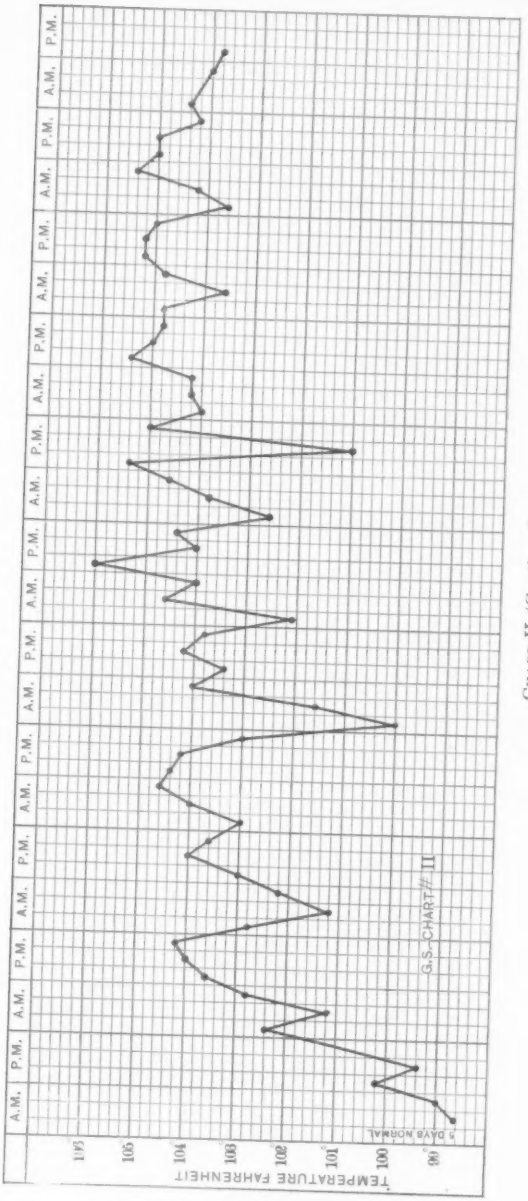


CHART II (Continued).

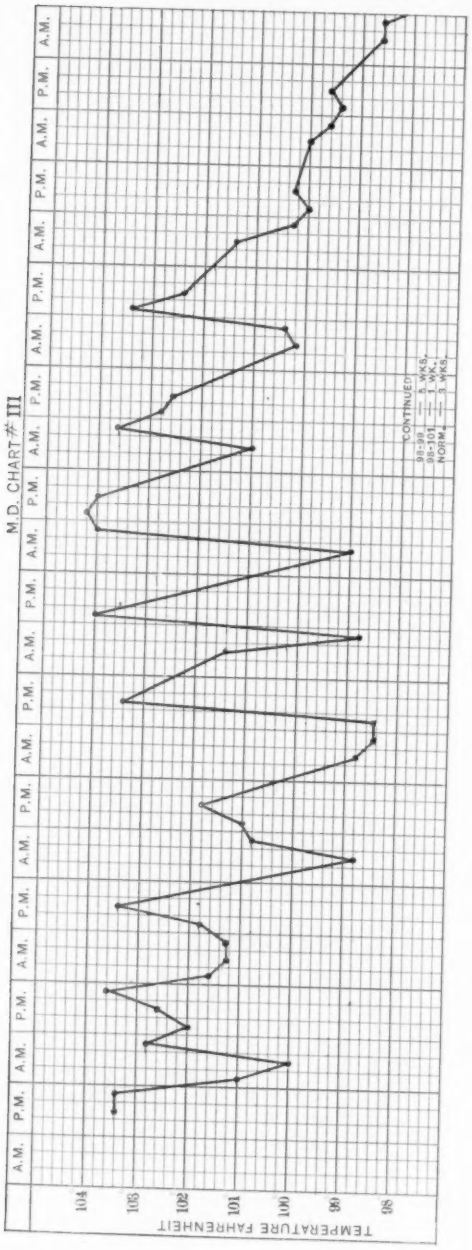

M.D. CHART # III
TEMPERATURE FAHRENHEIT
104
103
102
101
100
99
98
A.M. P.M. A.M. P.M. A.M. P.M. A.M. P.M. A.M. P.M. A.M. P.M. A.M. P.M. A.M. P.M. A.M. P.M. A.M. P.M. A.M.
CONTINUED
98-39
99-101
NORM.
1 WKS.
1 WK.
1 WKS.

CHART III

98°, 101°, 102°, with evening elevations, it being normal for one week before death.

The course represented in Chart IV is that of a female, aged twenty-four years, with an extensive cervical and axillary involvement. This was followed by periods of 99° to 101°, occasionally to 103°, but for three weeks before death was frequently subnormal. A case very similar but with more extensive axillary involvement for one week gave a temperature of 99° to 101°. Temperature taken frequently since has been normal. In the former case (Chart IV) the lungs, spleen, and kidneys were involved; in the latter case the left breast is diffusely hard and infiltrated, but there is no evidence of visceral disturbance.

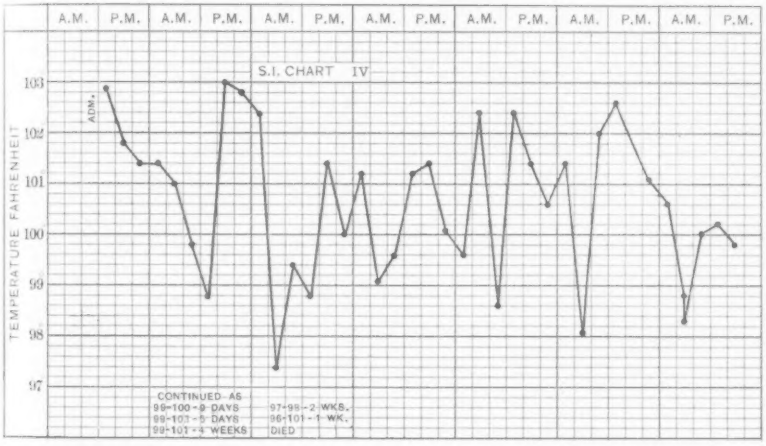


CHART IV

Why one case with a slight involvement and another case with an extensive involvement should show such diversity in toxicity and clinical findings could perhaps be best explained on the infectious theory. During the febrile attacks there is apparently no change in the pathology of the disease, but Zeigler suggests that these reactions are due to metastases to internal organs.

In five of the active febrile cases blood cultures were taken and were all reported negative. If the organism described as the etiology is responsible, no better cases could be obtained to rule out at least a septicemia. These cultures were made on the ordinary laboratory media grown aërobically. With the now improved technique along these lines and with enriched media, if there is an associated septicemia, it will not be long before it is worked out.

PHYSICAL STATUS. Seven of these patients were in good general physical health, showing nothing of importance except local conditions. In these the average duration of the disease was five months.

The most common physical signs exclusive of the specific trouble are referred to the lungs, *i. e.*, a few cases of marked recurring hydrothorax. One case was tapped six times and a cloudy straw- to amber-colored fluid obtained, showing 97 per cent. lymphocytes and 40 per cent. by volume of albumin; at the autopsy the lungs presented an extensive process of Hodgkin's disease. In another case the fluid obtained was of a greenish, milky color, with 400 cells per cm.; polynuclears 32 per cent., lymphocytes 68 per cent., pseudochylous fluid. A third patient whose sputum was negative for tubercle bacilli on four examinations, was tapped eleven times, the fluid varying from a light amber to a dark brown, containing few cells and 1.5 per cent. of albumin. The fluid is not diagnostic, as it closely resembles that seen in the exudation of tuberculosis. Two other cases gave signs of a dry pleurisy at the base, and one, suspicious signs of tuberculosis at the left apex.

Five of the cases showed markedly hypertrophied tonsils, and from these were elicited frequent attacks of tonsillitis. In two others the teeth and gums were in very poor condition. Pyorrhea in one case and a protracted stomatitis in another had been very troublesome.

In this connection it seems appropriate to refer to some recent work done on the bacteriology of cervical glands. From three cases of tuberculous lymphadenitis, one case of large round-cell sarcoma (primary mediastinal), one case of Hodgkin's disease, and one gland diagnosed by Bunting as a typical Hodgkin's picture, but by Warren, Mann, Butterfield, and the writer as a peculiar metaplasia, a diphtheroid organism has been obtained, closely related to, if not identical with, the so-called B. hodgkini of Negri and Miermet,[26] Fraenkel,[27] Bunting,[28] and others. A gland from an active Hodgkin's disease planted on favorable media, such as Dorsett's egg and glycerine phosphate potato agar, after three weeks' observation is still sterile. We are inclined to believe that this organism is not the specific cause.

THE PRESENT STATUS. The present status of the cases is as follows: 7 have died, 2 of these directly following operation, 1 of which died with the picture of acute toxemia. This case at operation presented two large retroperitoneal masses, and a section was removed for diagnosis. Patient returned to ward in good condition, but a few hours later was taken with a shaking chill, temperature 104°, and frequent projectile vomiting. The following day tem-

[26] Centralbl. f. Bakteriol., 1913, lxviii, 292.
[27] Münch. med. Wchnschr., 1910, lviii, 655.
[28] Arch. Int. Med., 1913, xv, 236; Jour. Amer. Med. Assoc., 1913, lxi, 1803; ibid., 1914, lxii, 516; Johns Hopkins Hosp. Bull., 1914, xxv, 173-177.

perature rose to 105.6°, followed by chill, collapse, and death. It was suggested at the time that operative interference may have liberated an excess of toxin, producing a condition analogous to postoperative thyrotoxicosis. The average duration of life in the other 5 cases was two and a half years, the longest being two years and eleven months and the shortest eight months.

Of the remaining 16 cases, 9 have not been heard from, 5 show recurrence or active manifestations, 1 is latent, and 1 is in good health. The average duration to date has been three years, exclusive of the one of twenty-five years' duration, the shortest one and the longest ten years. From present indications may of them will probably live a few years longer, but the prognosis of longevity in Hodgkin's disease is an uncertain factor even when there is an extensive involvement.

Since making these tabulations, Case 24, of twenty-five years' duration, shows remarkable change. The neck swelling has increased markedly, causing pressure on the larynx and trachea, and there is pronounced edema of the left arm and both legs. Fifteen years ago this patient received a Roentgen-ray burn, and on the advice of our roentgenologist, Dr. Leaming, this form of treatment is now contraindicated.

Microscopic Pathology. When one attempts to add anything to the microscopic pathology of Hodgkin's disease, little if anything will be new, for it has been very well covered by Reed, who made it what it is in this country. In the earliest description of this subject the original paper of Hodgkin, the gross appearance was completed by the term "cancer cerebriformis," unqualified but presumably because of the close resemblance to the gray matter of the central nervous system.

From the study of these cases it is my contention that the Dorothy Reed type is not a special form of Hodgkin's disease, but is the picture which makes Hodgkin's a distinct entity. Sections taken from various glands of a group enlargement give graded pictures from simple hyperplasia of lymphoid elements to the characteristic whirlwind fibrosis; but in some, if that group be the result of Hodgkin's disease, there will be that picture as described by Reed. It is a quantitative change, a stage not a qualitiative one. For this reason it is to be recommended that when one performs an operation in view of obtaining a gland for diagnosis, several glands should be excised as at either extreme a positive diagnosis is difficult. There is apparently no relation between the picture of glands and the clinical course of the disease. The so-called experimental Hodgkin's in the ape with its marked necrosis attributed by Bunting to the virulence of the infecting agent is something one rarely sees in human histology; but we occasionally see glands with marked endothelial hyperplasia and large areas of necrosis as the result of a pyogenic infection of low grade and of long duration. Over 125

sections taken from 23 cases have been carefully studied in this connection, and in only two specimens were areas of necrosis found. In these, two in each case, they were small, circumscribed foci of necrosis and polynuclear reaction.

To make different points clear, it is well to consider four stages which are by no means distinct but merge into one another imperceptibly in the same gland.

I. Hyperplasia of lymphoid elements.

II. Hyperplasia of endothelial elements with giant-cell formation.

III. Beginning fibrosis and loss of original architecture of gland.

IV. Fibrosis, atrophy of lymphoid elements, masking of characteristics.

The earliest pictures of Hodgkins disease are like those of any infection or irritation, a hyperplasia of lymphoid elements, and though the disease be suspected clinically, a histological diagnosis cannot be made, although "probably or suspected Hodgkin's" is justly resorted to. Sections from Cases 5, 6, 8, and 20 clearly demonstrated this point. In Case 5, with moderate enlargement of glands on the right side of the neck, many sections presented a hyperplastic lymphoid structure without other diagnostic features. This patient returned two years later with recurrence on the right side of the neck, and the glands were typically those of Hodgkin's with Reed cells, epithelioid cells, fibrosis, and eosinophiles. At the present writing this patient has a walnut-sized gland in femoral group and feels perfectly well.

From Case 6 another diagnosis of "suspected Hodgkin's disease" was made, and two years later the histology was unmistakable.

In Case 8 the examination of a small node offered nothing but hyperplastic lymphadenitis; the later examination of a larger gland gave a picture of moderately advanced healing. The histology of Case 20 had been particularly interesting. Several large areas of a nodular skin lesion had been excised and subjected to examination. All the earlier sections showed the same picture—fibroblastic reaction—fibrosis, round-cell infiltration, with a few eosinophiles and polynuclears and numerous small bloodvessels. Sections from glands gave a typical picture, and later sections from skin presented lymphogenetic areas with endothelioid cells and giant-cell reaction. This case demonstrates very well the primary compensatory lymphogenesis with subsequent involvement.

A point which appears to be of some value in this hyperplastic stage is the dearth or absence of the so-called germinal centres, for in glands of other sources they are of common occurrence. To conclude this stage it might be well to consider for a moment the derivation of the lymphocytes. The origin of lymphocytes under all conditions in health and disease is not known.

Fleming,[29] after demonstrating that efferent lymph was more

[29] Arch. f. mikr. Anat., 1885, xxiv, 70.

cellular than afferent, in a classical article, basing his observations from glands of lower animals adopted the term "keimcentrum" to designate the peculiar and variable collection of cells seen in the follicles. This work was done on normal lymphatic tissue, and it was concluded that lymphocytes were produced by proliferation of mother cells of centres which in turn developed from certain cells of reticulum. Cases 8 and 19 seem to support this view, showing, as they do, lymphocytes developing in the centre of these centres in small follicular collections. These are the only instances of the kind that I have seen or heard of.

That not all lymphocytes are developed from these germinal centres is supported by the following: (1) We occasionally see nuclear division in lymphocytes themselves; (2) they develop in certain regions of the body where there has never been any evidence of these centres, as in the omental fat, liver, lungs, and skin; (3) in certain glands definitely hyperplastic we fail to see germinal centres or their remains. Bearing on this point, Fleming believes that the "keimcentrum" is a transitory unit, increasing and decreasing, appearing and disappearing at intervals. Yet, on the other hand, in some glands the seat of chronic inflammation we see their remains as hyaline fibrous pearls; and in Hodgkin's disease in the early stages when the lymphoid hyperplasia is at its height these centres are rarely seen. Yet these glands continue to enlarge, the predominating cell is lymphocytic, but they have no germinal centres to take origin from; (4) some writers believe they are derived from endothelium.

Pari passu with the increase in lymphoid structure appears a hyperplasia of endothelium and endothelioid cells. The endothelium of sinuses shows marked proliferation and scattered throughout the glands in variable numbers are cells of endothelioid type. These are most prominently seen in the reticulum of glands where many mitotic figures are made out. This picture is present in all the glands of series. With these smaller cells are seen many large ones more faintly staining with large polychromatic vesicular nuclei, containing one to three nucleoli; the so-called endothelioid, epithelioid, or giant mononuclear cell. These cells are present in eighteen of the specimens and multiply in part by karyokinesis and in part by direct division. Owing to the distribution of these cells they apparently develop from the reticulum. But when one reviews the literature on this subject he hesitates to say that they do develop in this manner for there are as many theories as there are writers. Ziegler believes they are formed for the most part from typical fibroblasts, swollen pathological forms. Longcope is of the opinion that they are derived from the reticulum.

A cell which has been prominent in this series and referred to by Symmers, perhaps ordinarily termed a giant mononuclear cell, is a large very faintly staining cell with lobed and partially divided

pale nucleus. The protoplasm is not always clearly defined. We are beginning to place more weight on this cell, as it is quite as common as the Reed cell and seen many times when there is no evidence of the latter. We believe it to be a transition stage of the smaller endothelioid cells, these dividing by indirect division to produce like cells and by direct division the stage referred to to produce typical Reed cells. Transitions from the endothelioid cell to the Reed cell are clearly made out in the various sections. This is in contrast to Fabian, who believes they are formed from large lymphocytes, to Sternberg, Symmers, and Reed, who believe them formed from endothelium of sinuses, but conforms to the views of Longcope.

The Reed cells, giant multinuclear or sometimes termed mulberry cell, appear as a pathognomonic histological sign. At this date the description of such a cell is hardly necessary. In 17 of the 23 cases this cell has been found in varying numbers, containing from 2 to 10 nuclei of central and radial placement. In a few instances the nuclei have been of peripheral arrangement, simulating the architecture of the Langhans giant cell, but the morphology of the nucleus is distinctive.

Another cell type seen in one-quarter of the cases, which is very scarce and not of any value as an aid to the diagnosis, is a large clearly-defined cell with rather small deeply staining nucleus and large amount of eosinophilic protoplasm. They are seen occupying small spaces. The occurrence of eosinophiles in this disturbance was first noticed by Goldman,[30] who believed they were withdrawn from the blood by some specific chemotactic powers. This has been attributed by Bunting to the destruction of lymphocytes, polynuclears appearing in excess with the destruction of endothelium. Ziegler speaks of their presence being more common in the fibrosis. This conforms with Bunting's idea, and in reviewing the slides in this connection there seems to be this definite relation. They were present in large numbers in 50 per cent. of cases and absent entirely in six cases. Realizing that they rarely occur in large numbers in other conditions, and never in closely allied malignant states, their presence is of some significance by way of exclusion.

Plasma cells are commonly described as an important feature, but there seems to be a great diversity of opinion in the interpretation of the morphology of these cells. However, their presence or absence is of no diagnostic significance. In this study with the ordinary stains they were definitely made out in but a few instances.

The fibrosis manifests itself early in a thickening of the capsule and trabeculæ with a diffuse fibroblastic reaction and fine fibrillar fibrosis, the diffuse fibroblastic reaction being clearly made out at the onset of the endothelial reaction. As this process advances

[30] Centralbl. f. Allg. Path., 1892, iii, 665.

the preponderance appears to arise from trabeculæ, and in very late stages gives rise to a picture designated as whirlwind fibrosis. With the advent of fibrosis, lymphocytes become fewer and fewer, and though widely disseminated, there is in reality an atrophy.

The endotheliod cells in the same way give place to or in part give rise to the fibrosis. Bloodvessels become much thickened, and where there is a retention of germinal centres there is a central, intra- and perifibrosis. It is impossible to say whether the giant cells disappear entirely or give rise to the fibrosis. The glands lose their original follicular and characteristic pathological architecture, and the termination is a loss of the cellular fibrosis with hyalinization. This has been designated by Symmers[31] as "healing in Hodgkin's." The diagnosis cannot be made from such a gland or differentiated from the end-results of an acute lymphadenitis, tuberculosis, or syphilis. One, many, or all these gradations may be seen in one gland or its group.

In none of the cases has there been a clearly-defined picture of a transformed or superimposed malignancy. Case 23 was that of a middle-aged man, who had an axillary tumor of ten years' duration. At operation a massive axillary lymphatic involvement with direct extension into the pectoral muscles was found. The extension resembled in all respects the picture seen in the glands, lymphocytes with giant mononucleated and multinucleated cells and fibrosis. There is in this case, undoubtedly, one of the salient features of malignancy, but the histology remains typical of Hodgkin's disease.

Vaccines. In spite of the recent findings of an organism (isolated from glands, not Hodgkin's) similar to if not identical with the so-called B. hodgkini, several cases have been treated with vaccines.

Case 19 was operated on one year ago, and since this time has had energetic treatment (in the out-patient department) by a vaccine made from B. hodgkini obtained from the Museum of Natural History. He returned to the hospital a few weeks ago and several recurrent glands were excised. These were cultivated in the operating room under strictly aseptic conditions, on egg media, glycerin-phosphate-potato-agar, and the ordinary media, and all tubes were sterile at the end of one month.

Case 17 has been treated with vaccines and Roentgen-ray for one year. Although she feels in better health the glands are larger and the breast is infiltrated.[32]

Cases 16 and 24 have progressed with constantly increasing and long-continued dosage. They have had a fair trial, but since this organism is not the specific cause it seems futile and a waste of time and material to continue.

[31] New York Med. Jour., May 20, 1911.

[32] Under Roentgen-ray treatment alone all glands have reduced greatly in size, and the breast has returned to normal.

SUMMARY OF BLOOD FINDINGS. For this summary only those blood examinations which have been studied and later reviewed by Dr. Warren are considered. Several examinations were made on 10 of the cases, and the average is found to be as follows:

No.	Hb.	Red blood cells.	White blood cells.	Polymorphonuclears.	Lymphocytes.	Large mononuclears.	Transitionals.	Eosinophiles.	Basophiles.
4	70	4,150,000	74,000	91.7	3.3	2.3	2.4	.0	.3
6	60	4,300,000	15,000	76.8	6.7	0.8	12.6	2.3	0.5
11	75	5,600,000	20,000	80.0	11.0	1.8	6.0	0.5	1.15
15	58	3,500,000	14,000	69	20	2.3	7.3	1	0.3
16	68	4,360,000	12,000	68	22.3	2.3	5.0	2.3	0
17	80	3,750,000	11,000	78	11.5	3.3	5.8	0.6	0
18	90	5,550,000	19,000	72.5	19.6	0.6	5.3	1.3	
19	94	4,800,000	16,000	73.5	17	0.5	7.0	0.6	
20	56	4,700,000	62,000	92.0	1.5	2.3	3.5	1.3	0.15
24	68	4,000,000	12,000	71.0	15	5.3	6.3	1.5	0.6

With some of the other cases the hemoglobin has varied between 40 and 110 Sahli corrected and the red cells from 2,944,000 to normal. These two units vary directly with the course and severity of the disease, and are of no diagnostic importance.

The total leukocytic count and differential is a very variable factor. It does not seem to bear any direct relation to the duration of the process. Considering the microscopic pathology we fail to find evidence of acute inflammatory reaction (necrosis or polynuclear infiltration) in these cases with high leukocytosis. It is, however, dependent on the severity or toxicity of the case and remains high in this type of case when the temperature drops to normal. This leaves us to account for it for the greater part on the extent of involvement of the lymphatics and internal organs. Very good examples are offered in Cases 4 and 20, the former reaching 104,000 the latter 112,000. Both these cases presented an extensive general involvement. A leukopenia was observed in only one case (Case 10).

In the differential counts the polynuclears are relatively and absolutely increased, the lowest being 53 per cent. and the highest 97 per cent. Blood platelets are increased.

As seen in the table of blood findings the transitionals are found to be variable, though in general increased, in seven of these being over 5 per cent., the highest being 12.6 per cent., the average 6.6 per cent. The series is too small to lay too much stress on the diagnostic importance of a high transitional count, which is considered by Bunting to be diagnostic when accompanied by chronic lymphatic enlargement. We have recently had a case of primary large round-cell sarcoma of the mediastinum with extension to clavicular glands which gave a transitional differential of 13.3 per cent. A mistaken diagnosis from blood findings alone could easily have been made in this case. For years a relative lymphocytosis had been considered the usual finding, but none of the late reports

show this. In over 33 counts the average was 14 per cent., and 30 to 40 per cent. is unusual. The conclusions from such a small series are not of much value, for the picture is quite a variable one. The quotation of Fabian[33] in this particular seems quite appropriate: "The blood picture changes in one-fifth part of an observation."

No.	Case.	Adm. No.	Case index.	Path. No.	Result.
1	L. M.	...	May 24, 1909	286	Lost trace.
2	P. B.	B–1	July 18, 1909	588	Lost trace.
3	F. DeM.	B–181	Feb. 17, 1910	1910	Lost trace.
4	S. J.	B–257	Dec. 24, 1910	2056	Died.
5	H. S.	A–742	Aug. 18, 1910	3530	Living; recurrence.
6	M. D.	A–1439 D–3656 7736 5568	....	5503 8938	Died.
7	M. Gr.	D–1554	Feb. 11, 1911	.....	Lost trace.
8	J. C.	A–1819	July 19, 1911	6897	Died.
9	A. H.	D–1893	July 17, 1911	6572	Lost trace.
10	F. K.	B–2000	Oct. 10, 1911	7653	Died.
11	A. V.	H–2218	Dec. 25, 1911	8300	Lost trace.
12	Mr. F. P. P.	2888	Aug. 5, 1912	B–323	In good health.
13	G. S.	D–3998	.....	.....	Died (?)
14	G. S.	D–3998	Aug. 9, 1912	B–355	Died (?)
15	C. S.	A–4862	May 7, 1912	B–3183	Died.
16	W. B.	B–4380	Oct. 4, 1912	B–4529	Recurrence.
17	E. L.	A–5070	April 30, 1914	B–6581	Active.
18	P. B.	A–6036	May 18, 1914	B–6780	Lost trace.
19	A. B.	A–4987	May 19, 1914	B–6838	Active.
20	M. G.	A–2245	Sept. 28, 1911	7608 7675 7814 8744	Died.
21	P. Q.	B–6071	Mar. 4, 1914	B–7045	Died.
22	M. S.	D–6192	June 5, 1914	B–7028	Living (metaplasia).
23	D. C.		May 5, 1912	B–9606	Dead (?)
24	O. G.	A–5472	Dec. 1, 1914	B–8762	Active.

CONCLUSIONS. 1. Dorothy Reed Hodgkin's is not a type but the classical picture; it stands as a distinct entity.

2. The prognosis of Hodgkin's disease is difficult. It is impossible to say that a case is cured.

3. The treatment is excision of all foci of infection and Roentgen-rays.

4. Vaccines are of no value.

5. For diagnosis in lymphatic disturbances more than one gland should be obtained.

6. The following evidence is given to support it as an infection, bacterial or protozoan in origin: (*a*) the histology is that of an inflammatory reaction; (*b*) injections of gland emulsions have caused temporary lymphatic enlargement in lower animals (literature);

[33] Centralbl. f. Allg. Path., 1911, xxii, 145.

(*c*) the fever resembles closely that of other infections; (*d*) the leukocytosis; (*e*) the exudate when serous surfaces are involved.

7. The specific organism has not been isolated. A detailed report will appear later to support this.

In concluding, I wish to thank Dr. Warren and Dr. Mann who have made this work possibly by their stastistics and coöperation, and Dr. McCreery for his earlier work on the histories.

THE CITRATE METHOD OF BLOOD TRANSFUSION IN CHILDREN.

By Richard Lewisohn, M.D.,
NEW YORK CITY.

The citrate method of blood transfusion which I described in January, 1915,[1] has rapidly gained great popularity. Theoretical objections against the mixture of blood with an anticoagulating substance have been overcome by practical experience. This has proved that the citrated blood is clinically as effectual as pure blood. The great simplicity of the method, which makes blood transfusion technically as easy as an ordinary saline infusion, has, of course, widened the applicability of the former, even in smaller communities, and will certainly serve to popularize blood transfusion.

The effectiveness of citrate of soda as an anticoagulant is, of course, nothing new. In fact, we all know that for many years it has been used quite extensively in the laboratories for the purpose of preventing blood from clotting. The dose used for this purpose was 1 per cent.

I have often wondered why so much time has been spent in devising technically most complicated methods (vessel anastomosis, syringes, etc.) instead of applying this well-known drug in human blood transfusion.

The answer is given in the experimental part of my work, which I published in detail a few months ago.[2] These experiments brought to light two important facts:

1. That it is unnecessary to use 1 per cent. sodium citrate to prevent coagulation of the blood, but that 0.2 per cent. suffices.

2. That sodium citrate used at the ratio of 1 per cent. would prove fatal in large transfusions of blood (1000 c.c.).

This last fact answers the question why sodium citrate has not been applied before in human blood transfusion. The fear that this anti-coagulant might prove to be toxic when used in large doses is

[1] Med. Rec., New York, 1915, lxxxvii, 141.
[2] Surg., Gynec. and Obstet., 1915, xxi.

a well-founded one. That sodium citrate may be safely applied for intravenous injection of large quantities of blood, without risk or danger to the patient is based on the fact that my experiments showed that a mixture of 0.2 per cent. citrate of soda is sufficient to prevent coagulation.

These results of my animal experiments were of special importance on account of another publication on this subject which appeared contemporaneously with mine. Weil[3] reported that he had injected up to 350 c.c. of blood mixed with 3.5 grams of sodium citrate. He had used this large dose of citrate because, evidently through some error in his experiments, he had come to the conclusion that 1 per cent. sodium citrate (*i. e.*, the dose used in laboratory work) was necessary to prevent coagulation. There was no warning in his paper against the possible toxicity of sodium citrate at the 1 per cent. ratio. My animal experiments show conclusively that if anybody had applied Weil's dose for a large transfusion on the human being the results would have been fatal. The citrate method, which has proved harmless and efficient, when applied at the 0.2 per cent. ratio, would surely have been abandoned after a few trials if my experiments had not pointed out the toxicity of Weil's dose and thus prevented others from using citrate at the ratio of 1 per cent.

The atoxicity of sodium citrate at the 0.2 per cent. ratio (*i. e.*, 2 grams of sodium citrate to 1000 c.c. of blood) is best proved by the use of this method for transfusion of blood in small children. Blood transfusion in infants has great possibilities. Melena neonatorum, primary and secondary anemias, typhoid hemorrhages, some cases of marasmus, etc., yield remarkably well to blood transfusions and often show most startling results. All the older methods presented the greatest technical difficulties when applied in these little infants, and therefore blood transfusion has not been used sufficiently in small children.

The technic is exactly the same as described for adults.[4] The donor's vein can be punctured proximally or distally, the direction to be chosen according to the individual case, whichever way the blood runs with the greatest facility into the glass receptacle. The blood is mixed in the glass jar with a 2 per cent. sterile solution of sodium citrate at the ratio of 1 to 10 (*i. e.*, 10 parts of solution to 100 c.c. of blood). For the reintroduction of the blood a very fine needle or cannula can be chosen. Thus one can inject the blood even in small children through a superficial arm vein of the finest caliber. This obviates any extensive dissection. By using so fine a needle one assures the slow injection of the blood and prevents the danger of sudden overloading of the circulatory system. The salvarsan flask is attached to a stand and the blood

[3] Jour. Amer. Med. Assn., 1915, lxiv, 425; Clin. Conf., Mt. Sinai Hosp., Jan., 1915.
[4] Loc. cit.

allowed to run into the vein drop by drop (in 1 case the injection of 350 c.c. thus took nearly an hour, and the three-year-old child stood this rather large quantity of blood very well, just on account of the slow injection).

Among the 30 cases of blood transfusion in which I used the citrate method 7 were children.

The first child in whom the new method was applied was a boy, aged five years, with extensive burns. He received two transfusions of 150 c.c. of blood. His hemoglobin was raised from 42 to 72 per cent. The improvement in the general condition of the child was most remarkable.

The second case was a child, aged three years, with hemorrhages from the intestinal tract. This child received its first transfusion (Lindeman's method) in August, 1914. The hemorrhages then stopped for six months. The patient was readmitted to the hospital in February, 1915, on account of the recurrence of hemorrhages. A second transfusion of 200 c.c. of blood (citrate method) from the father of the child failed to stop the hemorrhages. An exploratory laparotomy was then decided upon, preceded by another transfusion of 450 c.c. of citrated blood. An exploration of the stomach and duodenum was negative. Two weeks later the hemorrhages began again, and since the child was very anemic, another transfusion was advised; this time the Unger method was used. The improvement following this transfusion was only temporary and a fifth transfusion (citrate method) was given in May, 1915. Since then the child has picked up wonderfully. The hemorrhages have stopped entirely. The child appears to be in perfect health; but palpation of the abdomen now reveals an enlarged spleen. This probably explains the hemorrhages from the stomach. This case shows how much can be accomplished by repeated blood transfusions. In regard to the new method it shows that citrated blood is as efficient as unmixed blood. The reason that the clinical result of the last transfusion was so much better than that of the three previous transfusions (two done with the citrate method and one with the Unger method), is probably based on the fact that the blood of the last donor was exceptionally well adapted for this child's blood. We know very little about the relative values of the blood of different donors. But it certainly is advisable, in cases where one transfusion failed to give good results, to try another donor.

The third case was a child, aged six months, suffering from an aplastic anemia. The child received two transfusions, each of 100 c.c. The baby had remarkably improved and showed an excellent color. The child was readmitted two weeks later on account of severe gastro-enteritis, to which it succumbed on August 15, 1915. In little infants a small amount of blood ought to be introduced repeatedly in order to safeguard against sudden overloading of the circulatory system.

The fourth case was a nine-months-old baby; the indication for transfusion was a severe anemia. The child received 100 c.c. of blood and the hemoglobin was raised from 16 to 26 per cent. The child's condition was decidedly improved. This was the only case in this series which had quite a severe reaction (rise of temperature to 102° F. without chill) following the transfusion.

The fifth case seems to me to be the most interesting in this series. A seven-year-old girl had profuse intestinal hemorrhages on the fourteenth day of typhoid fever. The hemorrhages were so profuse that the child was in a dying condition; she was unconscious and the radial pulse was not palpable. An immediate transfusion was done; the blood was taken from the mother; 400 c.c. of blood were transfused. The change in the condition of the child was most remarkable. She reacted while she was receiving the blood and the pulse reappeared. The hemorrhages stopped and no further bleeding occurred during the course of the illness. The disease ran a very severe course, and to combat the marked sepsis a second transfusion was deemed advisable. This was again done by the citrate method, three weeks after the first transfusion. The symptoms of severe typhosepsis were not changed by this transfusion and the child died seven weeks after the onset of her illness. It is interesting to note that this child had a very marked anaphylactic reaction after the first transfusion, though the blood was taken from the mother. No reaction occurred after the second transfusion, for which a professional had been selected and properly tested. This case tends to show that theoretical objections against citrated blood are not based on facts; on the contrary, the citrate transfusion ought to be the method of choice in hemorrhages, because the coagulation time of the recipient's blood is shortened immediately after the introduction of citrated blood.

The sixth case was a three-year-old boy, a hemophiliac, who was very much exansanguinated from a severe hemorrhage (bite o the tongue) which had lasted for twenty-four hours. He received 250 c.c. of citrated blood and the bleeding stopped immediately; his hemoglobin was raised from 19 to 39 per cent.

The last case, the youngest in this series, was a baby, aged twenty days, which had been bleeding since its birth from the umbilicus; 80 c.c. of citrated blood stopped the hemorrhages immediately and permanently; the baby was taken home a few days later.

REVIEWS

MODERN ASPECTS OF THE CIRCULATION IN HEALTH AND DISEASE. By CARL J. WIGGERS, M.D., Assistant Professor of Physiology in Cornell University Medical College. Pp. 361; 104 illustrations. Philadelphia and New York: Lea & Febiger, 1915.

THE ever-increasing knowledge of the physiology and the pathological physiology of the circulation, through the studies of both the physiologist and clinician, makes necessary a book or a monograph on the subject available to those who are unable to follow the large amount of literature upon the subject. To supply this need, Dr. Wiggers, long a student of the circulation, has brought out the present work. The monograph is divided into three parts: part one deals with the present-day conception of the maintenance of the circulation in health; part two describes the graphic methods of studying the circulation for the clinician; and part three correlates the first two parts with the simpler methods of diagnosis available at the bedside. With the subject matter arranged in this manner, one is enabled to follow readily the application of the physics of the circulation to pathological processes, so that the information derived thereby is of use in the study of clinical material. This book is not written solely for the man who wishes to be thought up to the minute, but is in truth for the man who wishes to know and to study a clear and thorough exposition of the modern concept of the cardiovascular system which has revolutionized this branch of medicine in the past ten years. One learns the rationale of the uses and the interpretation of the results from the use of the sphygmomanometer, the electrocardiograph, the phonocardiograph, the polygraph, and other instruments of precision employed in the study of the circulation. The aid that the work is bound to give those interested in clinical medicine will insure for it a marked success and a particularly hearty reception from those who wish to know exactly the whys and wherefores of the various procedures in the study of the circulation. J. H. M., JR.

SOZIALE PATHOLOGIE. VON PROF. DR. MED. ALFRED GROTJAHN, Berlin. Second edition. Pp. 532. Berlin: Verlag von August Hirschwald, 1915.

THE second edition of this work comes enriched by three years' experience the author has enjoyed while in charge of the Section

on Social Hygiene in the Hygienic Institute of the University of Berlin. While he has set himself a very ambitious task both as to size and complexity, he has performed it in a most interesting fashion, has furnished a great deal of valuable material, and, through the manner in which he has utilized this material to mould broad general concepts in regard to the relation between disease and social questions, has definitely supported his claim to originality.

The work contains two main divisions, a special and a general part. The first deals with a vast number of individual diseases, such as individual acute and chronic infections, circulatory diseases, respiratory diseases, sexual diseases, nervous and mental diseases, occupational diseases, diseases particularly affecting women, infants and children, surgical diseases, ocular diseases, and others. Each disease in turn receives a systematic investigation to determine social-pathological data, such as the frequency of the particular disease, the amount of disability and loss of income it occasions, the prevalence of slight and abortive forms of the disease, the broad etiology of the disease, entailing a consideration of habits nutrition, environment at home and at work, etc., the effect of the disease on social conditions, medical treatment, insurance, and, particularly, the social treatment and prevention of the disease.

This first part giving individual consideration to each special disease prepares the way for the second part dealing with problems of wider range. The relative importance from a social stand-point of different groups of diseases, and especially the great influence of the diseases of infants, children and women, the relation of the physician to social medicine, the relation of social status to disease, the results of disease, for example, in shortening life and in limiting income, are discussed. The value of segregation in the case of many diseases is emphasized. Problems associated with degeneracy and eugenics receive very special consideration. The author is particularly interested in the subject of the prevention of conception, first, as a preventive of the transmission of diseases or diseased tendencies, second, as a means in certain cases to obtain fewer and more vigorous offspring, and, third, as a real danger, if it is abused to the extent of unduly reducing the birthrate. A steadily falling birth-rate he considers far more destructive for the German race than even the war now raging between the Germans and the English. However, a falling birth-rate that may be detrimental to a nation as a whole at our present stage of uncivilization, is not demonstrated by the author to be necessarily injurious to the individual himself, except as a part of that nation.

It would be impossible to summarize the author's views or discuss his conclusions in a brief review. Many of the questions presented are, and will long remain, unsettled. In regard to many of the subjects in which science has clearly shown the path to follow, the difficult task still remains to see that the proper measures are carried out. C. M. M.

THE CLINICS OF JOHN B. MURPHY, M.D., at Mercy Hospital, Chicago. Vol. IV, No. 3, June, 1915. Pp. 196; 90 illustrations. Philadelphia and London: W. B. Saunders Company, 1915.

THE most important feature of this number of *Murphy's Clinics* is "A Clinical Talk on the Diagnosis of Injuries of the Carpus," a subject which fully justifies the addition of fifty-eight pages to the current literature. The more common injuries and their diagnostic signs are admirably presented from the stand-point of anatomic reasoning and are well illustrated by drawings and roentgenograms. The clinical aspects of four selected cases emphasize the possibility of accurate diagnosis and the necessity for appropriate treatment in a class of fractures and dislocations not infrequently neglected. In "A Talk on Appendicitis," Dr. Murphy makes the astounding statement that "the average hospital mortality rate is just a little over 10 per cent." The statistics are taken from the printed annual reports of hospitals, and include appendicitis cases of all classes. Dr. William J. Mayo gives a talk on "Unsuccessful Gastro-enterostomy for Ulcer: An Analysis of its Causes, Suggestions for Better Technic." His final statement, "Looked upon as a whole, I think nothing in the field of surgery has given such good results as the operative treatment of ulcer of the stomach and duodenum," suggests the thought that many surgeons will have to gain an experience with the more modern principles and master the best technic before they can share this optimism.

In the nine cases of various types with Dr. Murphy's comments and the descriptions of operations, the reader will find new ideas, and perhaps old ideas presented in a new way, in sufficient number to commend this number of the *Clinics*. G. M. L.

THE CLINICS OF JOHN B. MURPHY, M.D., at Mercy Hospital, Chicago. Vol. IV, No. 4, August, 1915. Edited by DR. P. G. SKILLERN, JR., of Philadelphia. Philadelphia and London: W. B. Saunders Company, 1915.

THE August number of *Murphy's Clinics* is edited by Dr. P. G. Skillern, Jr., of Philadelphia, and gives a summary of each case. There are thirty-two headings, an unusually large proportion of which deal with the surgery of the nervous system and are discussed by Dr. Mix. The summary will be found useful to the regular subscriber who cannot spare the time to read what had already been covered in previous numbers and the frequent references will enable the new reader readily to find the collateral subjects in former volumes.

The reviewer cannot feel convinced that treatment of the primary lesion of syphilis with sodium cacodylate masters the syphilis problem. In the case of papilloma of the bladder it is noted that the three glass test is dwelt upon as a method of determining the source of hematuria and that mention of cystoscopy is not made. In the case of "Typhoid Spondylitis in a Typhoid Carrier," drainage of a macroscopically normal gall-bladder and removal of a symptomless appendix furnish a striking illustration of how arthritis cases are handled. There are so few roentgenograms of typhoid spine on record that it is to be regretted that there is no mention of Roentgen-ray examination in this case. G. M. L.

APPLIED IMMUNOLOGY. THE PRACTICAL APPLICATION OF SERA AND BACTERINS PROPHYLACTICALLY, DIAGNOSTICALLY, AND THERAPEUTICALLY, WITH AN APPENDIX ON SERUM TREATMENT OF HEMORRHAGE, ORGANOTHERAPY, AND CHEMOTHERAPY. By B. A. THOMAS, A.M., M.D., Professor of Genito-urinary Surgery in the Polyclinic Hospital and College for Graduates in Medicine; Instructor in Surgery in the University of Pennsylvania; Associate in the William Pepper Laboratory of Clinical Medicine, and R. H. IVY, M.D., D.D.S., Assistant Instructor in Surgery in the University of Pennsylvania; Instructor in Genito-urinary Surgery in the Polyclinic Hospital and College for Graduates in Medicine, Philadelphia. Pp. 359; 5 colored inserts and 68 illustrations. Philadelphia and London: J. B. Lippincott Company, 1915.

UNLIKE the farmer's basket of apples, this excellent book presents its faults in the opening chapters and thereafter improves steadily in worth and lucidity to the end. At the worst the faults are not important and consist of a certain carelessness in writing, especially in the introduction, and at times of a lack of that proper distribution of emphasis which is so helpful to the uninitiated. Thus isocytolysins are mentioned impartially with toxins and agglutinins, and such subjects as the antityphoid extract of Jez, anticarcinomatous extracts, and the use of crotalin in epilepsy are enumerated merely to be condemned. Apparently the isolation of the rabies organism takes place between the twelfth and the sixty-fourth pages.

Unhesitatingly, however, it may be stated that the book succeeds most admirably in its object "to crystallize and detail the practical phases of serum and bacterin application in medicine, thereby enabling the student and general practitioner, with even

a slight laboratory experience, to appreciate the significance of, and more competently apply the principles underlying, immunology." No more satisfactory brief description of the Widal phenomenon, the Wassermann test, tuberculin tests and tuberculin therapy has been published. The opsonic index and bacterial inoculations receive attention disproportionate perhaps to the other chapters, but certainly not to the importance of these topics. Finally, the appendices, especially that on chemotherapy and the various necessary technics, add still further to the usefulness and value of this very satisfactory work. O. H. P. P.

Radiography, X-ray Therapeutics, and Radium Therapy. By Robert Knox, M.D. (Edin.), M.R.C.S. (Eng.), L.R.C.P. (Lond.), Hon. Radiographer, King's College Hospital, London; Director, Electrical and Radiotherapeutic Department, Cancer Hospital, London, etc. Pp. 406; 64 plates, 246 illustrations, and frontispiece in color. New York: The Macmillan Company, 1915.

The author of this admirable book is, by way of introduction, a well-known English roentgenologist whose talent is recognized on both continents. His connections with numerous hospitals and in the capacity of editor of the *Archives of the Roentgen Ray*, having recently succeeded Dr. Deane Butcher, are additional indications of his high standing among roentgenologists of his own country. The English language is lamentably weak in books on roentgenology, which are of use to those specializing in this branch or that can be safely recommended to those beginning a study of the subject, but this is one of the very best so far published in this language. It is concise and at the same time comprehensive, and with a very few exceptions is thoroughly up-to-date, embodying the most modern views and methods and showing conversance with the latest literature. It is a book that can be of service to the roentgenologist and radium therapeutist, and is one of the very few that may be recommended to the student with a view of supplying him with useful knowledge without fear that he may be misinformed or misled. A section of reasonable length is devoted to the description and use of different forms of Roentgen-ray apparatus and tubes, with, quite naturally perhaps, a decided leaning toward those of foreign design. One chapter deals with modern methods of localization of foreign bodies, which has become a most important use for Roentgen-ray work abroad during the past year. A very useful and instructive section is devoted to a roentgenologic study of normal bones and joints and of bone development. In his

presentation of gastro-intestinal diagnosis the author is extremely conservative, and possibly too much so, although he can hardly be criticised for this in view of the rapid strides being made in this department of roentgenology and the numerous and radical changes constantly being made in technic. The diagnosis of conditions of the thoracic viscera and urinary tract is far above any criticism. The entire diagnostic section is profusely illustrated by an excellent selection of reproductions, for the appearance of which the publishers deserve the greatest praise. About one-third of the book is devoted to roentgen and radium therapeutics. The author's description of roentgen technic is concise but thorough, and the freedom of the text from case reports is commendable. The section on radium therapy is preceded by a chapter on physics of radium, by Mr. C. E. S. Phillips. In conclusion, this book can be conscientiously recommended to roentgenologists for reference, to physicians and surgeons as a means of increasing their knowledge of the subjects discussed, and to the student in roentgenology as a text-book. H. K. P.

A Laboratory Manual and Text-book of Embryology. By Charles William Prentiss, A.M., Ph.D., late Professor of Microscopic Anatomy in the Northwestern Medical School, Chicago. Pp. 400; 369 illustrations. Philadelphia and London: W. B. Saunders Company, 1915.

"This book represents an attempt to combine brief description of the vertebrate embryos which are studied in the laboratory, with an account of human embryology adapted especially to the medical student." With these words, the author began his preface, and when one examines the worthy result of his efforts one is doubly regretful at the loss which American science, as well as his personal circle, has sustained in the author's death, shortly after the completion of this volume. In the introduction he urges the value of all well-preserved human embryos to the investigator, and suggests that aborted embryos and those obtained by operation in case of either normal or ectopic pregnancies should always be saved and preserved by immersing them intact in 10 per cent. formalin or Zenker's fluid. One might add that the history of the patient should be as complete as possible on all points pertaining to the age of the embryo. In Chapter I, in the description of germ cells and fertilization, reference is made to the substance, which F. R. Lillie has shown to be produced in the ova of the sea-urchin, and named by him fertilizin. This substance, Lillie regards as an amboceptor essential to fertilization, with one side-chain which agglutinates and attracts the spermatozoa and with another side-chain which

activates the cytoplasm and initiates the segmentation of the ovum. After describing the segmentation of the fertilized ovum in the several vertebrate classes (Chapter II), the study of chick embryos is briefly outlined in Chapter III. The stages selected are of twenty-five, thirty-six, and fifty hours' incubation periods, which are sufficient to show important stages in the development of the main systems, of body form, and of the membranes. Chapter IV is devoted to fetal membranes and early human embryos. Illustrations are given of several of the young embryos which have been carefully studied during the last few years, and the anatomy of a 4.2 mm. human embryo, studied and described by His, is given in some detail. Illustrations of twenty-five stages, up to the end of the second month, are shown. As to the method of estimating the age of young embryos, the author judges it more correct to compute the age from the end of the last menstruation, or even, according to Grosser, from the tenth or twelfth day before the first missed menstrual period. In Chapters V and VI the anatomy of pig embryos of especially 6, 10, 18 and 35 mm. length is described by the aid of dissection and serial sections. The author was well-known for his ability in dissecting these delicate objects, and has given a brief description of his method. The dissecting instruments include a binocular dissecting microscope and a sharp safety-razor blade, and the embryo must be hardened carefully to have the right consistency, neither too brittle nor too soft. In the remaining six chapters are given descriptions of the development of the various systems and organs of the human body. Frequent reference is made to recent work, and the numerous illustrations are drawn, for the most part, from the works of the main contributors to the science. Many of the descriptions are necessarily brief, but the text is always clear, and the book, as a whole, will surely realize its author's aim in usefulness to the student. W. H. F. A.

MEDICAL APPLIED ANATOMY. By J. B. JOHNSTON, M.B., CH.B., Lecturer on Anatomy, University College, London; lately Lecturer on Medical Applied Anatomy, Edinburgh Post-Graduate Courses in Medicine and Surgery. Pp. 436; 146 illustrations, and 3 full-page plates in color. London: A. & C. Black, Limited, 1915.

THE author of this work has endeavored to show the applications of anatomy to the study of clinical medicine, and while there are certain anatomical sections of the book which even by the widest stretch of the imagination, can have no possible direct relationship to internal medicine, still on the whole his efforts may be said to be

highly successful. In order to properly carry out his purpose the subject is treated according to systems rather than according to regions as is done with surgical applied anatomy. The first system discussed is the central nervous system and it comprises nearly half the book. Then follow chapters upon the organs of special sense, the digestion, the vascular, the respiratory and genito-urinary systems and the ductless glands. The anatomy of the various parts is described and with the anatomical description there is given a careful explanation of how this applies to physical diagnosis, what relation it has to the physiology of the part, how pathological changes effect the normal anatomy and physiology, how therapeusis changes normal or abnormal conditions and a multiplicity of other facts an explanation of which is extremely hard to find in ordinary text-books.

The book is intensely interesting and extremely practical. It is distinctly a border-line book which will fulfil a very definite purpose in linking more closely the science of anatomy with the art of internal medicine. J. H. M., Jr.

Lead Poisoning. By Sir Thomas Oliver, M.A., M.D., M.R.C.P., Consulting Physician, Royal Victoria Infirmary, and Professor of the Principles and Practice of Medicine, University of Durham College of Medicine, etc. Pp. 294. New York: Paul B. Hoeber.

This book is made up of a series of lectures delivered by the author in the Royal Institute of Public Health, Russell Square, London. He treats the subject of lead from the social and industrial points of view as well as from the medical, and does it all in such a simple and clear-cut way as to be entirely intelligible to both the laity and the profession. In the first portion of the book there are placed before the reader the various and sundry ways by which lead may gain entrance into the body; the details of the smelting, the manufacture of red and white lead, the dangers of the lead paints, of printing and type-founding, etc., all being covered. This is followed by a presentation of the symptomatology of lead poisoning, and finally in the last few chapters he discusses its treatment from both the preventive and curative points of view. As a curative agency he is quite enthusiastic about the electrolytic treatment, with which he seems to have experimented considerably. In an appendix of sixty pages he embodies the English factory and workshop orders relating to lead poisoning.

Oliver's experience with this metal, the most widely used metal but iron, has apparently embraced its every aspect, and he speaks largely out of this experience, at the same time presenting many statistics, tables, and opinions from other investigators.

T. G. M.

EDEMA AND NEPHRITIS. By MARTIN H. FISCHER, M.D., Eichberg Professor of Physiology in the University of Cincinnati. Second edition; pp. 695; 160 illustrations. New York: John Wiley and Sons, 1915.

THIS work is a combination of the author's two previous works upon *Edema* and *Nephritis* respectively, with certain additions particularly concerning the application of the colloid chemical theory to such fundamental physiological phenomena as absorption and secretion, hemolysis and muscular contraction. In calling attention to colloid reactions and to the probability that these reactions play an important part in many fundamental physiological phenomena, the book is of considerable interest and value, and will repay reading. It is unfortunate, however, that the author so frequently insists, quite without adequate proof, that these colloid reactions can be the whole explanation of these physiological and pathological phenomena. This practice renders the work to a dangerous degree misleading.

In discussing the treatment of nephritis with anuria or oliguria the author still recommends the injection of an alkaline hypertonic sodium chloride solution, a therapy against which exists the weight of repeated careful studies by many investigators upon the affects of sodium chloride in nephritis. Clinical and experimental studies emphasize the positive danger of chloride administration in many types of nephritis, especially in those associated with diminished output of urine and with edema. Indeed, this therapy is an illustration of the unfortunate errors that might spring from an unqualified acceptance of the theory advanced by the author.

J. H. A.

THE OPERATIVE TREATMENT OF CHRONIC INTESTINAL STASIS. By SIR W. ARBUTHNOT LANE, BART., M.S., F.R.C.S., Senior Surgeon to Guy's Hospital and Emeritus Surgeon to the Hospital for Sick Children, Great Ormond Street. Third edition. London: James Nesbit & Co., Limited. Chicago: Medical Book Co., 1915.

THE first chapter of this book contains the author's well-known views concerning the evolutionary development of the mechanism producing chronic intestinal stasis. He opens his discussion by noting the changes in the skeleton arising from strain and then proceeds to demonstrate that comparable alterations are found in the gastro-intestinal tract from like cause. The reader will be interested in the author's description of the ills that result from intestinal stasis as well as the remarkable changes that are noted after the colon has been removed. Although excellent results were reported in earlier papers following lateral and end-to-side anastomosis the

author has discarded these in favor of colectomy and end-to-end anastomosis. The technic of operation is fully described. It is to be regretted that in the last monograph, which stands as a *résumé* of his work, the author has failed to include a summary of the end results in all cases thus treated. The second and third chapters are written by Jordan and Mutch, and deal with the investigation of chronic intestinal stasis by the Roentgen-rays and the bacteriochemistry of the small intestine. A few pages are given to quotations from Mackenzie's *Diseases of the Heart*, showing that what he once termed "*X*-disease" is identical with chronic intestinal stasis. The final chapters contain two papers which the author published nearly thirty years ago and deal with skeletal changes incident to occupation. F. E. K.

THE HEART IN EARLY LIFE. By G. A. SUTHERLAND, M.D., F.R.C.P., Senior Physician to the Hampstead and North-West London Hospital; Physician to Paddington Green Children's Hospital. Oxford University Press.

SUTHERLAND has written a very readable book. As he himself says, he is clearly a disciple of Mackenzie and shares the latter's well-known optimism. As an illustration of this, one-quarter of the book is given up to functional disturbances of the heart, in which he goes into not only the question of functional arrhythmia but of functional dilatation, functional murmurs, and the subjective phenomena of cardiac disease, which very frequently depend on functional disturbances only. It seems well to dwell upon this subject at length, for no doubt not only the laity but many physicians have taken all murmurs and all irregularities too seriously. As to whether the placing of paroxysmal tachycardia in a section by itself designated "The Borderland between Functional Disturbance and Organic Disease of the Heart" is wise, may be questionable. Personally, the dogmatic separation of paroxysmal tachycardia and auricular flutter is at least clinically a useful division, but there are many who maintain that this division is quite unnecessary. However, Sutherland's division tends to emphasize the fact that in the majority of cases of paroxysmal tachycardia we are unable to point to a satisfactory cause. Here, perhaps, it is the limitation of our method of the minute study of the cardiac muscle and not the lesion that is lacking. The study of a few cases carefully and from many angles may be very instructive. Apparently this book has been written from such a stand-point. Though one misses the deductions drawn from a clinical experience which furnishes large groups of cases of a peculiar lesion or pathological activity, yet the material used is used well. C. A. F.

EVOLUTION AND DISEASE. By J. T. C. NASH, Captain, R.A.M.C., T.F., S.S., Diplomate in Public Health, University of Cambridge; Doctor of Medicine, University of Edinburgh, etc. Pp. 73. New York: William Wood & Co., 1915.

JUST as evolution has wrought changes in man's physical being so has evolution brought about variations in the diseases of man. The trend of the author's thought upon this matter is indicated in the following quotation from his chapter upon the evolution of disease germs: "I am not one of those who believe that disease germs entered one by one into the ark to transmit each its own species unchanged through the ages. It is very questionable if at that early stage of human history any pathogenic organisms existed, though probably their prototypes in the form of harmless saprophytes were to be found. As men began to crowd together . . . so gradually came into existence the necessary factors which resulted . . . in the evolutionized forms of organisms which are accountable for disease." With this idea in mind Nash has reviewed historically the epidemics of the middle ages. Following this he has dealt with some of the present-day scientific evidences of evolution in relation to disease. This contribution to the subject of evolution, while briefly stated, is broad in outlook, thought-producing, and gives one a larger and truer conception of disease.

T. G. M.

SIMPLIFIED INFANT-FEEDING. By ROGER H. DENNETT, B.S., M.D., New York Post-Graduate Medical School, etc. Pp. 355; 14 illustrations. Philadelphia: J. B. Lippincott Company, 1915.

THE author presents infant-feeding purely from the clinical standpoint, and by outlining but one method of procedure reduces the subject to the simplest possible terms. This will doubtless assist the beginning student to get a clear view of the fundamentals, but the general practitioner will regret the strict limitations of this book. Theories and generalities are almost entirely disregarded here and the directions given are explicit and specific. The addition of seventy-five case histories helps to elucidate the way in which the author puts his ideas into practice. Dr. Dennett is a strong advocate of the value of boiling milk, and he brings forward his experience on this phase of infant-feeding with much force of argument, which gives the work an unmistakable personal tone.

The chapter on proprietary foods brings together in one place, ready for reference, the analyses of these various foods, so that the busy practitioner may easily ascertain what any child may have been getting who has previously been fed on foods of this nature.

J. F. S.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF CLINICAL MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

ROGER S. MORRIS, M.D.,

FREDERICK FORCHHEIMER PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI, CINCINNATI, OHIO.

Vaccine Therapy of Typhoid Fever.—MEYER (*Berl. klin. Wchnschr.*, 1915, lii, 677) reports favorable results in 62 cases of severe typhoid fever treated by vaccine therapy. He found that the intravenous injection of a sensitized vaccine in the later stages of typhoid particularly tended to develop immunity. He believes that these injections are especially useful when applied during convalescence to prevent relapses and late sequelæ of typhoid fever.

Specific Treatment of the Malignant Forms of Malaria.—BASS (*Jour. Amer. Med. Assn.*, 1915, lxv, 577) says that the proper specific treatment of malignant or pernicious malaria is quinin administered intravenously. The dose and method of administering quinin intravenously are important. Bass does not believe that it is ever necessary to exceed 30 grains of quinin hydrochlorid during twenty-four hours when administered intravenously. He emphasizes the point that a single dose should never exceed 10 grains of the hydrochlorid. Large doses of quinin given intravenously are very dangerous. Twenty grains often produce considerable shock, dizziness, nausea, etc., and a dose of 50 grains has killed in several instances. Bass believes that 10 grains of quinin hydrochlorid given intravenously every eight hours or 5 grains every four hours will kill plasmodia in the blood stream and prevent their reproduction as certainly as any larger quantity and will not endanger the life of the patient. The author discusses briefly the subject of malarial hemoglobinuria. In malarial hemoglobinuria, red cells containing plasmodia, and thus damaged, are affected more certainly and more extensively than the normal cells. As a result they are hemolyzed, leaving the plasmodia they contained exposed

to the plasma, which promptly destroys them. The only object of giving quinin in malaria is to destroy plasmodia, and if most or all of the plasmodia have disappeared, which is the case in hemoglobinuria, there is no indication for quinin. There is a certain amount of contra-indication, however, because quinin tends to increase hemoglobinuria or to precipitate attacks in otherwise susceptible individuals.

Contribution to the Pathology of the Blood in Chronic Lead Poisoning.—SEHNITTER (*Deutsch. Arch. f. klin. Med.*, 1915, cxvii) draws the following conclusions after studying tbe blood of 196 cases of lead poisoning: (1) Basophilic stippling of the red cells is always present in chronic cases. (2) There is no constant relation between the degree of blood changes and the severity of the clinical manifestations. In general, however, they are roughly parallel. (3) The anemia present is most apt to be of the chlorotic type. (4) In a progressive intoxication, polychromatophilia appears first, followed by stippling. As the poisoning progresses, anisocytosis and reduction in the number of red cells may become very marked and is frequently associated with varying numbers of normoblasts, which may occasionally occur in crises. (5) A completely aplastic blood picture, such as is seen in benzol poisoning almost never occurs. (6) Most cases are associated with a moderate leukocytosis, which indicates a better prognosis than in those associated with a leukopenia. (7) The differential count shows a lymphocytic increase which may include the large mononuclear and transitional cells. The platelets are usually enormously increased. (8) Severe blood changes require six months to a year for complete restoration.

The Estimation of the Rest N. in the Blood as a Method of Testing Renal Function.—H. HOHLWEG (*Mitt. a. d. Grenzeb. d. Med. u. Chir.*, 1915, xxviii, 459), in association with Meyer, was among the first to demonstrate the value of determining the rest N. of the serum in the diagnosis and prognosis of severe nephritis. In the present communication, he reports observations on the rest N. of the serum of patients with uni- and bilateral kidney disease, before and after operation. He found normal values in pure unilateral disease and no increase following nephrectomy if the remaining kidney was normal. In patients with one diseased kidney and a toxic injury in the other, the rest N. is increased. Values up to 75 mg. for 100 c.c. of serum do not contra-indicate operation and in general indicate that the process in the good side is still reparable, or at least capable of improvement. Values of 100 mg. contra-indicate operation. The rest N. may increase just after operation but in four to six weeks it returns to its original level and may go lower than normal.

The Value of Uric Acid Determinations in the Blood.—Within recent years Brugsch and Schittenhelm have asserted that normal blood contains no uric acid. Its presence they consider as pointing to the existence of gout. FOLIN and DENIS (*Arch. Int. Med.*, 1915, xvi, 33) point out the fallacy of Brugsch's clinical method for the demonstration of uric acid by means of the well-known phosphotungstic acid reagent. It should be remembered that all blood contains varying amounts of phenols which also give a blue color with the above reagent, in fact

in some cases the amount of color produced may be two or three times greater than that given by the uric acid present in the blood. Folin and Denis are convinced that all short-cut methods so far proposed for the clinical determination of the uric acid in the blood are bound to give grossly misleading results. They have found by their method that normally uric acid is present in from 1.5 to 2.5 mg. per hundred cubic centimeters, and that in gout, lead poisoning, leukemia and some cases of nephritis, these amounts may be greatly increased. As a result of their study of several hundred uric acid determinations, made on many different kinds of human blood, Folin and Denis have become convinced that even exact quantitative uric acid determinations are not by themselves an adequate protection against frequent mistakes in the differential diagnosis of gout and other joint diseases. From tables which accompany the present article it will be seen that to be of material help in the differential diagnosis of gout, the uric acid determinations must be accompanied by determinations of the non-protein nitrogen. For any joint disease other than gout it is by no means uncommon to find uric acid values nearly, if not quite, so high as in gout. In arthritis, however, a high non-protein nitrogen is more frequent than a high uric acid, thus resembling frequently the blood from a case of glomerular nephritis. In addition to the determination of the uric acid and non-protein nitrogen, the patient must be put on a purin-free diet for at least two days before blood is withdrawn for analytical purposes.

Clinical Value of Diastolic Blood-pressure Determinations.—WARFIELD (*New York Med. Jour.*, 1915, cii, 509) is of the opinion that far too little importance is generally attached to the determination of the diastolic blood-pressure, and emphasizes the fact that pressure determinations in general, to be of any real value, should always include the systolic, diastolic and pulse pressure. These three constitute what he chooses to term the "pressure picture." After a brief discussion of the various opinions regarding the exact time at which the diastolic pressure should be read by the auscultatory method, Warfield points out the following clinical facts in support of his contention that the estimation of the diastolic pressure is more important than that of the systolic: (1) The diastolic pressure is more constant in individuals than the systolic. (2) Since it measures peripheral resistance, it would seem to be a more accurate index of either high or low tension than the systolic pressure. (3) A gradually rising diastolic pressure is of more significance than high systolic pressure. (4) Pulse pressure can only be accurately determined when the diastolic pressure is carefully measured. Large pulse pressures are apparently essential for the compensation of hypertension cases, while falling pulse pressures in such cases, indicate a failing heart. A pulse pressure below 30 mm. of mercury must be regarded as low, those above 50 as high. (5) The diastolic pressure should be taken by the auscultatory method at the sudden transition from the loud third tone to the dull fourth tone. Since the disappearance of all sound so closely follows the fourth tone, the diastolic pressure can safely be taken at that point. (6) Accurate determination of either systolic or diastolic pressure cannot be made upon decompensating hearts.

Our Present Knowledge Concerning Leprosy.—McCoy (*Am. Jour. Trop. Dis. and Prev. Med.*, 1915, iii, 83) says that the organism described by Kedrowski fifteen years ago, and believed to be the cause of leprosy, has been cultivated by a great many observers and in a variety of different ways. In addition to this acid-fast bacillus, diphtheroid organisms have been grown so many times from leprous tissues that the relationship of this group to the bacteria of the disease in question still demands an explanation. A tremendous number of attempts to reproduce the disease in lower animals have been futile. Indeed some 50 instances in which human bodies have been inoculated with leprous tissue tend to prove that this is an entirely safe procedure. This failure to produce an undoubtedly infectious disease with the acid-fast bacillus of leprosy, has naturally led to the suspicion that some other organism is the causative agent, but as yet it has not been demonstrated. There exists no support of Hutchinson's theory of the relation of the disease to fish-eating. Complement-fixation tests are generally positive and specific when the sera of the lepers are tested against antigens prepared from extracts of lepromas. The same sera very frequently bind complement when tuberculin is used as an antigen; finally, between 40 and 90 per cent. of all lepers give a positive Wassermann reaction, though they consistently give negative results with Noguchi's luetin test. All of these biological reactions are most pronounced in cases of the nodular type. At the present time we are still in ignorance as to how the disease is conveyed from person to person, or where the organism sojourns outside the human host. The bacillus doubtless escapes through open lesions of the skin and mucous membranes, but is probably never present in any of the excretions or secretions of the body. Healthy "nasal carriers" have been repeatedly observed. The studies of Hollmann go far toward disclaiming the role of heredity in the etiology of this disease. No positive diagnosis of leprosy should be made without the aid of microscopic examination of some of the tissues. Vaccine and antisera have thus far been of little value in treatment. Practically the only remedy giving favorable results is chaulmoogra oil. It is doubtful if any cases are ever cured. The protection of the community practically resolves itself into segregation of the afflicted.

The Lymphocyte and Natural and Induced Resistance to Transplanted Cancer.—Murphy and Morton (*Jour. Exper. Med.*, 1915, xxii, 204) report the results of their observations on the changes in the number of circulating lymphocytes in experimental carcinoma in mice, and the relation of this lymphocytosis to immunity. The basis for these observations appear in earlier communications in which the authors noted that adult animals deprived of most of their lymphoid system by Roentgen rays, no longer resisted the growth of heterologous tissues. The animals were divided into three groups: (*a*) Those having a natural immunity. (*b*) Those in which immunity was induced by the subcutaneous or intraperitoneal injections of a small amount of homologous living tissue at least ten days before inoculating the cancer graft. (*c*) Susceptible animals not naturally immune nor rendered so by previous treatment. In the first two groups (*a* and *b*), a definite lymphoid crisis occurs in the circulating blood within twenty-four hours after the introduction of the cancer graft which does not

take. In control animals in which the tumor grows, there is no such lymphoid response, while the polynuclear cells show a tendency to increase. Additional experiments show that this lymphoid reaction is not merely an accompanying factor in the immune period, but is essential to it. This is shown by the fact that destruction of the lymphocytes by Roentgen rays causes a loss of this natural or acquired immunity, thus rendering these animals susceptible to the tumor graft. In these cases, of course, there is no lymphoid response following the inoculation.

SURGERY

UNDER THE CHARGE OF

J. WILLIAM WHITE, M.D.,

FORMERLY JOHN RHEA BARTON PROFESSOR OF SURGERY IN THE UNIVERSITY OF PENNSYLVANIA AND SURGEON TO THE UNIVERSITY HOSPITAL,

AND

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY AND ASSOCIATE IN SURGERY IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL HOSPITAL AND ASSISTANT SURGEON TO THE UNIVERSITY HOSPITAL.

The Immediate and Late Disturbances from Kulenkampff's Anesthesia by Injection of the Brachial Plexus.—SCHEPELMANN (*Deutsch. Ztschr. f. Chir.*, 1915, cxxx, 558) says that during the past year and a half he has anesthetized the upper extremity by Kulenkampff's method in 300 cases and among harmless symptoms, has observed many times, arising suddenly, very disturbing symptoms which deserve consideration. Kulenkampff's technic was followed closely. By experimentation on rabbits Schepelmann found that injection of large doses of sinecain, cocain, or novocain, produced very severe cerebral symptoms. In cadavers he injected the brachial plexus with a methylene blue solution and found that by injecting exactly into the nerve sheath, the methylene blue extended itself under the spinal dura mater upward and downward over wide distances, many times upward as far as the brain. Aside from the harmless Horner symptom-complex (contraction of the lid-cleft and pupil of the same side, sinking backward of the eyeball, redness and sensitiveness of the conjunctiva), there were observed in 4 of the 300 cases more or less marked dyspnea in consequence of injuries of the pleura. In one case pneumothorax developed and twice, at first, alarming but transitory cerebral disturbances. Altogether there were 7 cases in connection with which disagreeable immediate effects were recorded. If, however, narcosis had been substituted for this method, at least, as many cases with disagreeable disturbances would have been met among patients with recent wounds calling for anesthesia without a preliminary preparation of the gastrointestinal tract. The Kulenkampff method should not be employed

where milder local anesthetic methods would suffice. It should be employed, however, where these methods are not sufficient, as in extensive suppurations and inflammations, major operations on the hands and arms, reduction of fractures and dislocations, and in amputations and excisions. It is especially desirable when Esmarch's method of hemostasis is employed. On the other hand, Schepelmann regards the double-sided plexus anesthesia as an unjustifiable procedure, because of the possibility of wounding both phrenic nerves, pleural cavities and lungs and thereby inducing very severe or fatal results. He has not observed any evil effects from frequent repetition of the plexus anesthesia at intervals of about eight days. A puncture of the subclavian artery with a fine needle is not considered serious, while the subclavian vein is too deep to be injured.

Comparison of the Secretion of the Two Kidneys in Dogs.—LEPINE and BOULUD (*Jour. d'urolog.*, 1915, vi, 297) made a study on dogs of the comparative excretion of the two kidneys. They did not find, as maintained by some writers, that the secretion of the two kidneys balance each other. The average for the right was somewhat greater than for the left, but when the dogs were perfectly normal the difference between the two sides was not marked. If one kidney is secreting against a moderate counter-pressure (30 to 40 c.c. of water), the quantity of water and chlorides excreted during this counter-pressure is sensibly less than on the opposite side where the escape is free. This diminution is due in part to an increase of the intrarenal absorption of water and chlorides. Consecutively, to an obstruction of one ureter of less than fifteen hours' duration, the water and chlorides are excreted in relatively greater abundance because of the diminution of the absorption by the functionally altered kidney. Unilateral intoxication of a kidney by the penetration of a few cubic centimeters of saline solution with the addition of quinin sulphate in the proportion of four parts to a thousand, produces a chloruria which may be excessive and is explained by a great diminution of the intrarenal absorption of the chlorides.

Gall-stone Disease.—DEAVER (*Ann. Surg.*, 1915, lxii, 197) reviews the case records of gall-stone disease operated on in his clinic at the German Hospital during the year 1914. The cases presented numbered 159, 87 of which are classified as simple gall-bladder disease, including types of cholecystitis with or without stones; 20 cases of gall-bladder and common duct involvement; 52 cases of gall-bladder disease with secondary pancreatic involvement, and 7 reoperative cases. Gall-bladder disease is preëminently a disease of the middle-aged female, but is by no means confined to that age or sex. The early diagnosis can be made only by familiarity with a different symptomatology than that found in the text-books. The lighter grades of dyspepsia with localizing signs, however slight, in the epigastrium or right hypochondrium must be regarded as very suspicious of the beginnings of gall-stone disease. Infection as the cause, not only of gall-stones, but of the local and systemic damage of the disease, is the essential thing to recognize and treat. The Roentgen-ray in diagnosis is dangerous, not only because it fails to show a large percentage of stones, but

because it emphasizes the importance of the calculous element of the disease, and if allowed to serve as an indication for operation will deprive many of the early treatment which alone is safe and efficacious. Cholecystectomy is the operation of choice in obviously diseased gall-bladders, with drainage of the common duct in practically all cases, but particularly in those giving evidence of cholangitis or pancreatic involvement.

Paget's Disease of the Nipple and Allied Conditions.—Jopson and Speese (*Ann. Surg.*, 1915, lxii, 212) say that Paget's disease of the nipple is a primary affection beginning in the cells of the rete Malpighii potentially malignant, although lacking the ordinary characteristics of malignant disease. It is identical with the disease known under the name of Paget occurring in other regions. It is commonly, although not invariably, followed by glandular carcinoma in the underlying breast tissue. It is precancerous in the sense that it induces epithelial changes in the superficial milk ducts and acini, which are followed by carcinoma. Occasionally, although rarely, it is followed by squamous cell carcinoma of the nipple. The disease is characterized by edema and vacuolization of the prickle cells, thickening of the rete, and active mitosis, also by an inflammatory reaction in the corium and a secondary hyperplasia in the milk ducts. It is sharply differentiated from true eczema and scirrhus carcinoma ulcerating at the nipple, and should not be confused with superficial metastases of diffuse cancer situated near the skin. The resulting tumors of the breast and the regional metastases resemble the type of breast cancer usually encountered. When the tumor originates in the skin, it infiltrates and metastasizes in the form of squamous carcinoma. The common association of cancer in the breast with Paget's disease demands as the treatment for Paget's disease the radical operation which is practised in breast cancers in general.

Second Report of the Committee on the Treatment of Structural Scoliosis to the American Orthopedic Association.—(*Amer. Jour. Orthop. Surg.*, 1915, xiii, 6). The committee offers the following summary as the result of its investigation of a second series of cases: (1) No case of overcorrection of the elements of deformity in structural scoliosis has been presented to the Committee, in which they have been permitted to observe and record the condition of the patient from a time preceding the beginning of treatment. (2) The time allowed by the Committee has been sufficient, in their judgment, for such a demonstration, were it possible in the respective patients and by the respective methods. (3) The same statements may be made with respect to complete correction of the elements of the deformity. (4) The amount of correction demonstrated to the Committee by means of the method of Forbes is unsatisfactory and is to be regarded as entirely insufficient reward for the amount of labor, discomfort and other inconvenience which is involved. (5) In mild cases of undoubtedly structural scoliosis, and perhaps in some moderately severe cases, considerable degrees of correction may be achieved by means of the method of Lovett and and by Kleinberg's brace. (6) It seems probably that greater degrees of correction may be obtained with the flexed position of the spine than

with the extended position of the spine. (7) It does not appear that the use of extreme force is justified by the results which are to be obtained from it. (8) In order to have reciprocal application to the given case, all records should be made with the patient in the same position; this refers to the clinical, photographic and roentgenographic record and to the horizontal or upright position of the patient. (9) For purposes of record the upright position is to be preferred.

Radium Treatment of Inoperable Uterine Cancer.—A report upon this subject recently published by NEWCOMET (*New York Med. Jour.*, 1915, cii, 19) strikes a decidedly pessimistic note, at least so far as any results that can be shown are concerned. Whether this may be due to to the rather small amounts of radium used (10 to 40 mg.) the author does not state. The paper is based on the last 50 consecutive cases of uterine carcinoma treated at the Oncologic Hospital, Philadelphia. Unfortunately no distinction is made between cervical and fundal cancer. About half the patients were under forty-five years of age; all were in more or less advanced stages of the disease, the condition being practically inoperable in most of them. In not a few instances the operable stage had been passed, not from any neglect or unwillingness of the patient to undergo operation, but because the symptoms were so slight as not to attract the woman's attention. In 3 cases the condition followed so closely upon a recent labor that the bleeding was considered merely a lochial discharge, while in one the first warning of anything wrong was the passage of fecal matter through the vaginal fistula. The 50 cases are classified into the following six groups: (1) Patients who left the hospital while under treatment, 4 cases. (2) Still under treatment, 2 cases. (3) Died while under treatment or subsequent observation, 14 cases. In most of these, death occurred within a few months of coming under treatment, and in all the disease apparently followed its natural course, uninfluenced by the radiation. (4) Unimproved, 24 cases; these patients have left the institution and have ben lost sight of; probably most of them are dead. (5) Improved, 11 cases; while in many instances the improvement was temporary, these patients did at least get some apparent relief for a time. (6) Greatly improved, 5 cases; in these the disease process diappeared, and was not detectable upon local examination; only one of these was an unoperated case, however; this was a woman, aged seventy years, with a very slow growing type of carcinoma; the other four had early recurrences following operation. The hemostatic action of radium, which has been so much insisted upon by almost all writers, was seen in most instances, but two women died of sudden violent hemorrhage coming on within a month or six weeks from cessation of treatment. In some instances there was relief of pain, but in a large proportion no influence of this kind could be noted, and some patients even complained of increased pain after exposure to radium. A number showed increased mental excitement, loss of sleep, and in three instances acute mania developed. The technique consisted in the introduction of a metal capsule containing the radium into the vagina for from three to eight hours daily, every other day, or at longer intervals, the duration frequency of treatments being governed by the amount of reaction obtained. Burning was always avoided, and no sloughing ulcers were produced.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

PROFESSOR OF CLINICAL MEDICINE IN THE COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, NEW YORK.

Salvarsannatrium.—GUTMANN (*Berl. klin. Wchnschr.*, 1915, lii, 400) writes concerning salvarsannatrium, which is a derivative of old salvarsan, so prepared that when dissolved in distilled water, its solution have the same chemical composition as solutions of old salvarsan prepared in the ordinary way by neutralization with sodium hydrate. The chief advantage of salvarsannatrium is the great simplicity of the technique of preparing the solution for injection, the new preparation being as easily soluble in water as is neosalvarsan. It is claimed, therefore, that salvarsannatrium combines the advantages of simple technique of administration of neosalvarsan while retaining the full therapeutic effect of old salvarsan. Salvarsannatrium is a yellowish powder which oxidizes readily on exposure to the air. The oxidized product is markedly toxic and, for this reason, solutions for injection must be made immediately before using. Gutmann recommends the method of Dreyfus who advises dissolving the dose in 20 to 30 c.c. of doubly distilled sterile water and injecting this intravenously by the syringe method. Gutmann advises a dose of 0.6 gm. for men and 0.45 gm. for women. During a period of six or seven weeks' treatment from 4 to 6 gm. can be given without untoward symptoms. A rise of temperature usually follows the intravenous injection. This promptly subsides and cannot be avoided. Skin eruptions of various types have also occasionally followed salvarsannatrium injections but are of short duration. No serious untoward symptoms have followed the use of salvarsannatrium in Gutmann's experience.

Immediate Results of Splenectomy in Pernicious Anemia.—LEE, VINCENT, and ROBERTSON (*Jour. Amer. Med. Assn.*, 1915, lxv, 216) report a series of 5 cases of pernicious anemia treated by splenectomy. The immediate results in this series were a prompt postoperative recovery and a definite remission of the disease in every case. The remissions were much more marked than are usually seen in pernicious anemia. In 4 of the 5 cases the red blood cells rose to from 4,000,000 to 5,000,000. However, in spite of the marked improvement, the blood picture retained the characteristics of pernicious anemia with the exception of a change in the color index from high to normal or low. Furthermore, in 3 of the 5 cases, evidence of increased blood destruction was present several months after splenectomy, as shown by the urobilin estimation. The authors cannot state that the improvement following splenectomy will last longer than the remissions which come spontaneously, and which may persist over a period of years. The only conclusions which the authors are willing to draw

from the cases reported by them combined with the reports of other writers are: (1) Splenectomy is not a very serious operation in pernicious anemia, and it offers a definite means of inducing a remission. (2) The remission thus brought about is more marked in the majority of the cases than any other known therapeutic procedure.

Recent Experiences in Vaccine Treatment.—MADDEN (*Lancet, London*, 1915, clxxxix, 267) prefers to use an autogenous vaccine, as a more potent and direct vaccine is made available. The strength of vaccine is generally 250 million to 1 c.c., with an initial dose of 50 million. The interval between the doses depend upon the case itself and the reaction produced, but they are never less than five days. The general effect of an appropriate vaccine, according to Madden, is to produce a definite reaction with fever and malaise and usually also a distinct but temporary exacerbation of the symptoms of the condition under treatment. When this degree of reaction occurs the injection should be carried steadily on in increasing strengths at proper intervals. The maximum curative effect is generally gained in from 8 to 12 injections. Madden has employed vaccines systematically in the treatment of boils and furunculosis generally. So universally successful has this method been in his hands that he never employs any other. A start is made with 100 million followed by 500 million five days later, and at a similar interval by 1000 million. Generally this series of three injections suffices to cure in the ordinary case; but in more intractable cases a further series working rapidly up to 5000 million, will almost certainly be sufficient. He has also had some success in cases of pyorrhea alveolaris with an autogenous vaccine, but he advises that vigorous local treatment must be carried out at the same time. In acne the results have been on the whole very disappointing. Compartively recent and uncomplicated pustular acne does, however, react very promptly in almost the same degree as an inverterate furunculosis; but in old cases, in which there is much scarring about the sebaceous follicles, results are likely to be disappointing. A further very important use of vaccines, Madden says, is in boils, carbuncles, and cellulitis occurring in diabetes. Here particularly one must make a practice of giving large and repeated doses of vaccines, alternating in extreme cases with antistreptococcic serums. Septic infection from operation wound or injury may also be controlled by vaccines; but it is very necessary to make sure of the causal organism before beginning a series of injections. Madden points out that in all vaccine treatment it must be remembered that an incision into the affected part acts like a vaccine, as it produces a phagocytosis which will itself have a vaccinal effect; quite apart from the evacuation of pus and septic serum and the relief of tension by the incision. Care must therefore be taken not to give a strong dose of a vaccine at the same time as the incision or too violent a reaction may occur. Further, vaccine must not be given during the stage of depression or of anaphylaxis resulting from the vaccinal effect of the incision. Madden states that he knows of no better treatment for infection of the urinary tract due to colon bacilli than that by vaccines, although treatment has to be long continued and relapse may occur. With respect to vaccine treatment of gonorrhea and its complications he has found that results have been very disappointing when the gonococcus

infecting organism. Certain cases of mixed infection respond to the is the principal proper vaccines. Pneumococcic vaccine, either as stock for acute lobar pneumonia or as an autogenous vaccine in cases of old chronic cough, especially if consequent upon a former inflammation of the lungs, is most useful but should not be depended upon entirely.

The Use of Digitalis in Various Forms of Cardiac Arrhythmia.—CHRISTIAN (*Bost. Med. and Surg. Jour.*, 1915, clxxiii, 306) says that an important indication of the beneficial action of digitalis is the decrease in the pulse deficit, *i. e.*, the difference between the apex beat and the radial pulse. In auricular fibrillation the counting of the radial pulse may be very misleading, it often being within normal limits when actually the heart is beating very rapidly. Digitalis impedes conduction in the bundle of His, and the result is that fewer auricular contractions send impulses through to originate ventricular contractions and consequently the ventricle beats more slowly. With slower contraction of the ventricle, there is more time for the ventricle to fill and more time for the muscle to recover from fatigue. Digitalis also probably exerts an action on the myocardium, causing more forcible contractions, and improves coronary circulation. In some patients with auricular fibrillation in which edema is marked, a much better diuresis is obtained by combining with the digitalis a diuretic drug, such as theocin. In another form of arrhythmia, namely, auricular flutter, digitalis usually produces a striking effect. The heart in such cases may slow down directly into a normal rhythm with great improvement in the patient's condition, or the digitalis may throw the auricle into fibrillation and when digitalis is stopped the normal rhythm is restored. In pulsus alternans digitalis frequently produces good results. In the rapid, regular, decompensated heart digitalis slows the rate by increasing vagus inhibition and by increasing conduction time between auricle and ventricle, and it strengthens heart action by some direct action on the myocardium and coronary circulation. This type of case often seems definitely resistant to digitalis and the patient may take large amounts before any effect can be detected. It is always well to remember in such cases to watch the patient carefully for sometimes the digitalis action, which has been long delayed, develops with great rapidity into marked activity so that the patient, who shortly before has shown no digitalis effect, quickly develops toxic symptoms. In paroxysmal tachycardia there is little evidence that digitalis produces any good effect. In sinus arrhythmia and in compensated hearts with ectopic beats or extrasystoles digitalis is not indicated. In cases of heart block not of digitalis origin, digitalis should be tried if the patient is decompensated. Results are sometimes good; at other times it would seem that the patient is made worse. Christian advocates the selection of one good digitalis preparation for administration by mouth and one for intravenous use. By continued use of the same preparations it is easier to estimate in a given case whether digitalis is effective or not. He deprecates the great number of "improved" preparations of digitalis as too confusing for proper judgment of effects. He prefers to use powdered digitalis or a freshly made infusion for oral administration and liquid digipuratum for intravenous use. Occasionally strophanthin intravenously is indicated but due regard must be paid to the

necessary caution against strophanthin in a patient who has been taking digitalis by mouth. As to dosage Christian says that relatively large doses should be used in periods of decomposition. With compensation restored very small doses continued over long periods certainly seem to be of great help in maintaining compensation.

The Inactivation of Pepsin by Sodium Chloride; Its Clinical Significance.—HAMBURGER (*Arch. Int. Med.*, 1915, xvi, 356) describes experiments that constantly showed that the neutralization of gastric juice results in complete inhibition of peptic action even after the addition of hydrochloric acid in excess, and that the inhibition of pepsin is due to sodium chloride acting in a neutral medium. The clinical application of these findings would lie in the ability to adapt measures whereby the stomach acid could be completely neutralized and the neutral reaction continuously maintained, and also that the newly formed and secreted acid could be immediately and continuously bound with alkali as soon as it was formed. If this could be accomplished, the pepsin set free by neutralization, as well as the newly secreted pepsin, would be bound by inhibiting sodium chloride and permanently inactivated. As a result, peptic activity would be destroyed for a period of time equal to the continuance of the neutral reaction, a condition similar to achylia gastrica. Such a temporary achylia would be desirable: (1) as a prophylactic measure, to prevent the formation of gastric or duodenal ulcer; (2) to facilitate the healing of ulcer by removing the factor which, next to mechanical trauma, is probably of greatest importance in the continuance and progression of chronic ulcer. Therefore in simple hyperacidity, in hypersecretion from whatever cause, in motor insufficiency with continuous secretion, in pylorospasm with hyperacidity and hypersecretion, in chronic ulcer, in gastro-enterostomy to prevent the formation of jejunal ulcer. Neutralization with peptic inactivation might be desired. The author states that by the use and combination of certain alkalies with certain foods and methods of feeding, continuous and complete neutralization of the stomach contents can be maintained.

The Treatment of Heart Disease.—SHATTUCK (*Bost. Med. and Surg. Jour.*, 1915, clxxiii, 316) presents the general principles of the treatment and management of patients suffering from cardiac disease with especial reference to the treatment of angina. He emphasizes that the all-important therapy of angina, whether grave or relatively benign, is the regulation of the mode of life. Every effort should be made to avoid bringing on pain. Shattuck points out that the details of medicinal treatment of true angina depend somewhat on its origin—whether this be infectious or non-infectious, and if infectious whether of syphilitic or other origin. Medicinal treatment is usually of minor, though still of real importance. Strychnia is to be avoided as tending to heighten reflex excitability. Digitalis is indicated only so far as myocardial failure is suggested by symptoms other than pain. Small doses of potassium iodid can seldom be harmful and seem to be of value even in non-syphilitic cases. The action of glonoin is so transitory that its value between attacks is doubtful. If it be desirable, as Shattuck believes to be rarely the case, to try to secure constant reduction of blood pressure, sodium nitrite or erythrol may be used.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND FREDERICK O. WAAGÉ, M.D.,
OF PHILADELPHIA.

Camphor Abscess.—VOGT (*Monatschr. f. Kinderh.*, 1915, xiii, 381) reports the great frequency of abscesses following the subcutaneous injection of camphor-oil in sick children in the pediatric wards of a hospital in Magdeburg. He mentions the possibility of some peculiar constitutional condition of the children of that part of the country making them more susceptible to the development of such lesions than the children of other parts of the Empire. These abscesses were so frequent that the technique of the subcutaneous injection, the asepsis and the material used was inspected and regulated with the utmost thoroughness, with no result in the diminution of the number of abscesses resulting. Also the abscesses were found for the most part to be sterile, a very few showing organisms which proved to be mostly staphylococci. The larger abscesses, even though sterile prove an unfavorable factor in seriously ill children. Abscesses opened during life or at autopsy showed the camphoric odor and large quantities of oil-droplets to have persisted a long time after the injection. It would then appear that the oil produced an irritation in the tissues and by remaining there for a long time acted as a foreign body. Camphor itself has irritating properties and causes locally more or less pain with subsequent redness and inflammation. It is noteworthy that the many injections of digalin and caffein employed in these cases resulted very rarely in abscess formation. In the development of abscess in the various cases there was apparently no relation the state of nutrition, the amount of subcutaneous fat, the severity of the general condition or the presence of edema. From this experiment it would seem that under certain conditions the subcutaneous injection of camphor may be attended by serious injury.

Clinical Distinctions between Cerebral Intoxication, Meningism, and Meningitis.—HEIMAN (*Arch. Pediat.*, 1915, xxxii, 579) discusses the clinical distinctions between meningitis and conditions with which it is often confused. Cerebral intoxication is a condition produced by absorbtion of toxins from physicochemical or bacterial agents or from animal or vegetable matter and characterized by irritative phenomena such as delirium, involuntary muscular movements, etc., and is fairly frequent in severe infections. Meningism, so-called serous meningitis, is a morbid process resembling meningitis in its manifestations but in which the spinal fluid is sterile. Cerebral intoxication is most strikingly illustrated in severe cases of pneumonia and typhoid fever, with delirium, photophobia, retraction and rigidity of the neck and twitching of the muscles or convulsion. Autopsy generally shows no lesions of the cerebrospinal system. There is always an etiologic factor to which the meningeal signs are secondary and the signs are significant of a

general cerebral irritation, while primary meningitis offers in addition focal signs, ptosis of the eyelids, strabismus, unequal pupils, etc. Lumbar puncture in intoxication shows the fluid sterile and clear with no variation from the normal cytological count while in meningitis various changes are present from the normal. Meningism indicates a greater degree of cerebral toxemia than is shown in cerebral intoxication and differs only by exhibiting increased intracranial pressure and a symptom-complex which still more simulates true meningitis. Its causes may be classified as infectious or toxic, irritative, reflex and hysterical. Under the first head acidosis and the later stages of gastro-interitis are most frequent causes. Of irritative causes head injuries, subacute and chronic ear conditions, and operations on the cranium, are found. Helminthiasis is included as a possible factor under reflex causes, and the hysterical types are cases claimed by the French to be occasionally mistaken for tuberculous meningitis. In meningism there is an etiological factor, the symptoms are transitory and subside with improvement in the etiological condition. The ophalmoscopic findings are negative and ocular changes rare, a slight congestion of the disks occasionally ocurring. The bacteriological and cytological differences in the spinal fluid must, of course, be regarded as the most important differential signs.

The Sex Distribution of Rickets.—PRIESTLY (*Brit. Jour. Child. Dis.*, 1915, xii, 173) reports several studies made during routine medical inspection in schools to determine the sex distribution in rickets. The total numbers of cases were rather constant from year to year, being 0.25 to 0.14 per cent. during the last five years. Out of a total number of boys and girls examined, 75,000, rickets appeared in boys 2.04 per cent., and in girls 1.13 per cent. This shows a difference in the incidence of rickets or rather post-rickety deformities, between boys and girls which is not quite in ratio of 2 : 1. In minor cases of rickets the same general effect is observed and in observing 5000 cases the boys were found to have 27 per cent. and the girls 16 per cent. The disease therefore seems more prevalent in boys than in girls, and should be included with rheumatism, pulmonary tuberculosis, and the graver nervous affections among the diseases whose incidence is considerably influenced by sex.

Aborted Pneumonia and Mistreatment of Pneumonia.—EPSTEIN (*Pediatrics*, 1915, xxvii, 70) criticizes the frequent diagnosis, "A touch of pneumonia," made by some physicians. A lobar pneumonia may be of short duration either because the different pathological stages are shorter or because the pneumonia terminates without passing through all the stages. These short pneumonias are rare and above the diagnostic ability of the average physician. Usually an "aborted pneumonia" is really some other known or unknown infection. Much is written on the treatment of pneumonia, but little is said of the mistreatment of the disease. As there is no specific treatment for the pneumonia the patient should be mainly treated and not the disease. Mistreatment consists of either too little attention, as in giving an ultra-homeopathic dose of some medicine and neglecting the patient, or in over-medication with all kinds of irritating drugs and nauseating

syrups, such as ammonium carbonate, etc. The best treatment is to conserve the child's strength and energy and to combat unfavorable symptoms. Hydrotherapy, proper feeding and plenty of fresh air with a temperature not too low in asthenic cases is of prime importance. The drug treatment can be divided into three classes—catharsis, diuresis and diaphoresis, and cardiorespiratory stimulation.

A Clinical and Pathological Study of 100 Infants.—Smith and Cobb (*Archiv. Pediat.*, 1915, xxxii, 434) present the data of two summer's work on the Boston Floating Hospital. The pathological findings represent a check on the clinical diagnosis of the various groups studied. Three main groups of digestive disturbances are noted as indigestion, indigestion with fermentation, and infectious diarrhea. Indigestion is from overfeeding of some food element or errors in feeding and the majority of cases recover. The autopsy findings in 25 cases of this group showed the gastro-intestinal tract normal in one-half the cases with the other half showing conditions from marked congestion to follicular and ulcerative enterocolitis. In the group called "indigestion with fermentation" the etiology is not clear, probably simple digestive disturbance and an infection enter into the condition which is of short duration, marked prostration and green, mucous or bloody stools. Of the 7 cases of this group coming to autopsy the majority showed nothing more advanced than congestion or catarrhal inflammation; only 1 case showing necrosis. In the third group, "infectious diarrhea," the etiology is bacterial, the clinical picture is the same for different organisms and the symptoms are of two types, digestive such as vomiting and diarrhea, and toxic, as high fever and prostration. In infection by the Flexner bacillus lactose solution is favorably employed, but in infection by the gas bacillus, feeding high proteid and low carbohydrates, as lactic acid milk is more favorable. Of the 40 cases coming to autopsy in this group 17 had follicular enterocolitis with necrosis, 9 had ulcerative enterocolitis or typical dysentery, and 7 had membranous enterocolitis, showing that the severe types of lesion predominate.

The Gas Bacillus and Infectious Diarrhea in Childhood.—Sylvester and Hibben (*Archiv. Pediat.*, 1915, xxxii, 457) describe their investigation of digestive disturbances caused by the gas bacillus and the treatment based on scientific study. Their investigation embraced infectious diarrhea, fat intolerance, carbohydrate intolerance, and chronic intestinal indigestion (marasmus). The test for the gas bacillus was based on the gas-forming properties of the bacillus in a carbohydrate media at suitable temperature and was therefore either positive or negative in any one case. The number of cases investigated were 172, of which 100 were positive and 72 negative. Infectious diarrhea showed 38 cases positive and 9 negative. Fat intolerance, 29 positive, 3 negative. Carbohydrate intolerance, 3 positive. Acute intestinal indigestion, 5 positive, 2 negative. Chronic intestinal indigestion, 15 positive, 4 negative. Breast-fed children under two weeks old, none positive, 30 negative. Controls made at frequent intervals showed that tap water, throat sticks and soap used for suppositories were uniformly negative. The Bacillus aërogenes capsulatus is generally

distributed in soil, milk and sewage, but is not a normal inhabitant of the intestinal tract of healthy breast-fed infants, nor was it found in 30 breast-fed infants under two weeks of age examined by Sylvester and Hibben. The gas bacillus grows luxuriantly on a high carbohydrate medicine and lactic acid is inimical to its growth and reproduction. It is advised in the treatment of these disorders to give a 5 per cent. lactose solution until a positive diagnosis is made of the presence of the gas bacillus by bacteriological examination. If the diagnosis is positive for gas bacillus unpasteurized, fat-free lactic acid milk is given and all carbohydrates are withdrawn. This is preferred to the administration of lactic acid bacilli culture.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

Birth Palsy.—PLATT (*Brit. Med. Jour.*, May 8, 1915) states that there are two theories to explain birth palsy. In one the paralysis is primarily due to stretching or tearing of the brachial plexus, by the other theory the primary lesion is one of the joints or bones, and the nervous lesions and symptoms are secondary. The cases usually follow a difficult labor, one arm of the infant hanging limp and motionless. The arm hangs close to the side with internal rotation at the shoulder, the elbow extended, the forearm pronated, fingers flexed and sometimes wrist-drop. The neck and shoulder may be tender for a few days. In many cases rapid and complete recovery follows, rarely no recovery or arm remaining practically useless, while in a considerable number partial recovery takes place. Shortening of the tendons and capsule of the shoulder-joint and about the other joints is present. In cases which do not completely recover subluxation of the shoulder-joint is often associated with birth palsy.

So far as treatment is concerned, as soon as possible after birth the arm must be fixed in a position to relax the paralyzed muscles. A splint or plaster-of-Paris brace is necessary. The splint consists essentially of a broad body piece and a narrow arm piece, suitably padded and furnished with webbing, straps, and buckles. This position of relaxation must be constantly kept up night and day. In addition daily massage and passive movements at the shoulder should be begun. When the patient begins to recover she must have exercise to train the muscles. Massage to be of use must be superficial and carried out with the muscles kept constantly relaxed. The splint must be used until the power of active external rotation and abduction at the shoulder has returned. If, after three months, the paralyzed muscles give the reaction of degeneration to electrical tests, operation should be performed. The writer does not speak enthusiastically of operation. As the

nerves are small it is difficult to dissect them out completely and to close them accurately. Should anastomosis be made it must be at the periphery. As a rule these patients recover, for it is very rare to see an adult who shows the results of birth palsy in infancy. Where the shoulder is deformed by internal rotation and the case has been neglected for several months, the position of the head of the humerus should be carefully ascertained, and if no subluxation is present, an anesthetic should be given, the contracted capsule stretched and the limb placed in the position first used in a splint or plaster. If the capsule cannot be stretched, an open operation with division of the contracted tissues is indicated. Where there is posterior subluxation of the shoulder-joint, the effort should be made under anesthesia to reduce a subluxation by manipulation. Should this fail, after two years of age an open operation is indicated, approaching the joint by the anterior route and dividing the anterior capsule and subscapularis tendon. It may be necessary to partially remove the acromion. Plaster-of-Paris should then be applied. Fixation is indicated for three months, followed by massage and movements.

Complete Inversion of the Uterus, with Prolapse and Recovery.—STEWART (*Brit. Med. Jour.*, June 26, 1915) reports the case of a primipara, delivered with forceps without especial difficulty. The uterus contracted well, and ten minutes after the birth of the child the placenta was about to be expelled. When this was removed the uterus was found completely inverted. There was practically no hemorrhage, but the placenta was somewhat adherent. It was detached and the effort made under chloroform to reduce the inversion for twenty minutes. This was followed by profound collapse and the effort was abandoned. Under stimulation the patient slowly rallied and was removed to a hospital, where, under anesthesia, the inversion was reduced by taxis. The patient's convalescence was prolonged and complicated, but she finally regained complete health. In reviewing this case, it must be noted that the placenta is said to have been "somewhat adherent," and also that in ten minutes after the delivery of the child the placenta appeared in the vagina. We question very much whether there was any real adhesion of the placenta, but the abnormality lay in the fact that sufficient time did not elapse after the birth of the child, before efforts were made by the patient or the physician to remove the placenta. From twenty minutes to a half hour should elapse after the expulsion of the child, while the mother remains perfectly quiet, before efforts are made to deliver the placenta. The placenta does not separate immediately, and as in this case, there is sufficient cohesion between the placenta and uterine wall to favor the inversion of the uterus.

The Intolerance of the Fibroid Uterus to Twin Pregnancy.—MONTUORO (*Ztschr. f. Geburtsh. u. Gynäk.*, 1915, lxxvi) reports three cases of twin pregnancy, complicated by fibroids of the uterus, in which abortion had occurred or the patient had to be operated upon for hemorrhage with threatening symptoms. He has collected from the literature fifteen other cases, and his own experience and statistics show that when twin pregnancy occurs in the fibroid uterus but 27.07

per cent. go on to viability or near term; 16 per cent. abort and between 55 and 56 per cent. come to operation. The period of pregnancy in which abortion usually occurs varies from the third to the sixth month. Twin pregnancy seems to stimulate fibroids to very rapid growth, while on the other hand the growth of the embryos produce great distension of the uterus, especially in the tissues in the region of the fibroids. This paper is valuable in forming a decision as to the treatment of such a case. It is useless to wait for pregnancy to develop to full term and the rule should be that twin pregnancy and fibroid uterus is best treated by prompt hysterectomy.

The Treatment of Placenta Previa.—STRATZ (*Ztschr. f. Geburtsh. u. Gynäk.*, 1915, lxxvi) in his Clinic at the Hague follows Schroeder and Hofmeier in his belief that combined version, followed by spontaneous labor or very slow extraction is the best treatment for placenta previa. He endorses in full Schroeder's statement that the best results in the treatment of placenta previa will be obtained if little consideration is given the interests of the child. By such a method infant mortality will not be excessive, while the maternal mortality will be much lessened. Stratz has treated 173 cases, of whom the greater part were private patients. There were 63 cases of deep insertion of the placenta, in which hemorrhage ceased so soon as the membranes were ruptured. In 110 combined version was practised. He made no difference between central and lateral placenta previa, but made his diagnosis from the fact that on vaginal examination the os was practically filled with placental tissue. Of the 173, one mother in the Polyclinic practice died, a mortality of 0.6 of 1 per cent. This patient gave birth spontaneously, after version, to a living child, but a half hour after the placenta had been expressed, sat up in bed suddenly, collapsed and died. At autopsy an open sinus the size of a little finger was found in the uterus at the contraction ring. The hemorrhage preceding the patient's death was not excessive, and embolism was the most probable cause. In 50 patients there was moderate elevation of temperature. In 3 there was pronounced infection, 2 having purulent endometritis, 1 had pelvic abscess which ruptured spontaneously into the rectum. These 3 cases had been tamponed by the general practitioner in attendance. All three recovered. Seventy-seven of the children were stillborn, and 20 had been dead for some time before birth. This makes a total fetal mortality of 45 per cent. The writer quotes the statistics of placenta previa for the year 1914 in Holland. The number of cases reported is 881, with a maternal mortality of 7 per cent. and a fetal mortality of 43 per cent. In those clinics where combined version is used as a method of treatment, 236 cases are reported, with a maternal mortality of 2.7 per cent. and a fetal mortality of 68 per cent. Embolism is a not uncommon cause of death following placenta previa, probably because of the unusual development of bloodvessels in the lower portion of the uterus. Stratz believes that where the bleeding is slight, the patient should be put at absolute rest and given narcotics. The tampon should be completely abandoned as a method of treatment and interference practised as rarely as possible. Where hemorrhage is considerable, combined

version bringing the child down sufficiently to check the hemorrhage, and if possible spontaneous expulsion should be procured. Under especially favorable circumstances, where the birth canal is dilated and the child not large, it may be very carefully extracted. The use of the dilating bag is unnecessary in most cases of placenta previa. Cesarean section he thinks is indicated only when a living child is earnestly desired, or in the presence of other complications.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Etiology of Adnexal Inflammation.—In a recent article NEISSER (*Med. Klin.*, 1915, xi, 511) calls attention to the fact that ever since the discovery of the gonococcus in 1879 some difference of opinion has existed between the andrologists—among which he classes himself—and the gynecologists as to the etiology of adnexal inflammations. He says truly that most gynecologists take the standpoint that when a hitherto healthy woman, whose husband has passed through an attack of gonorrhea at some previous time, develops within the first year or so of married life, or after her first pregnancy, an ascending endometritis and adnexitis, it goes without question that the latter is gonorrheal in origin, no matter how many repeated examinations of the husband have failed to demonstrate the presence of gonococci. Neisser says that he cannot agree with this viewpoint, for he believes that in many of these cases there may not be a true gonococcal infection. He says that this point has assumed a more practical interest than it formerly possessed since the introduction of modern immunotherapy, which requires for its successful application a determination of the specific organism at fault. He thinks that many of the failures reported from the use of gonococcal vaccines in cases of this type are probably due to the fact that the infection is not gonorrheal at all, but that other organisms may be responsible. These may be forced into the uterus by douches given under too high pressure. Moreover, it is well known, he says, that in every case of postgonorrheal urethritis in the male, quantities of bacteria of various kinds are harbored in the urethra long after the gonococci have entirely disappeared, and he suggests the possibility that in some cases some of these organisms may cause inflammation of the female organs. He admits that examination of organisms of this type has failed to show any marked pathogenicity so far as the ordinary laboratory animals are concerned, but this does not prove that they may not possess this property when in the human mucous membrane. He thinks the problem can be definitely solved only by careful and extensive bacteriological investigations by andrologists and gynecologists working together, but that in the mean-

time, we should be a little slower in jumping at conclusions that may mean the wrecking of a marriage until we are a little more sure of our ground.

Treatment of Carcinoma of the Uterus by the Percy Cautery.—This method of treatment for inoperable carcinoma of the cervix consists, as we brought out in discussing it a few months ago, in the utilization of a heavy cautery, of not sufficient heat to cause any charring of the tissue, but merely to thoroughly cook the whole area, as it were, by a degree of heat high enough to destroy malignant cells, without devitalizing healthy tissue. Heretofore most of the literature upon the subject has come from Percy himself, but a recent article by BALFOUR (*Jour. Lancet*, 1915, xxxv, 347) gives a preliminary report on 31 cases treated at the Mayo Clinic from January 1914 to June 1915. As Balfour emphasizes, of course nothing can be said as yet as to end-results in these cases, but the immediate effects have been so favorable that he feels the method has a very distinct field of usefulness. In all the patients there was immediate cessation of bleeding and discharge, with corresponding improvement in the general condition. Upon reëxamination six weeks to three months after operation, one generally finds a greatly increased mobility of the uterus, with an atrophic, clean, smooth cervix and vaginal vault. So far Balfour has not, as a rule, considered it advisable to give more than one cauterization treatment in each case. In nine instances a radical hysterectomy was subsequently performed, and in five of these careful pathological examination of the removed specimen failed to reveal the presence of any malignant tissue. The author admits the possibility that in some of these a primary hysterectomy might have been done, but he considers the preliminary heating of undeniable value in borderline cases. Destruction of the cancer cells themselves is not the only advantage of this: in from two to three months the shrivelled cervix in a scarred, firm vaginal vault, which has resulted, makes it possible to do a much cleaner and more satisfactory operation; the foul, infected tissues of the cancerous cervix are sterilized, and the very important factor of bacterial infection, which is largely responsible for the primary mortality of this operation, is removed. In a few cases complications were encountered, such as vesical fistulæ, late secondary hemorrhage, and implantation metastasis in the vagina. With increasing experience in the technique, however, Balfour thinks that most of these may be avoided. In the latest publication on the subject by PERCY himself (*Amer. Jour. Obst.*, 1915, lxxii, 298) many interesting and important details of his technique are described, with numerous illustrations of his instruments and method of arranging the patient for the vaginal and abdominal work. Percy does not hesitate to repeat the cauterization four or five times on the same patient, if necessary, opening the abdomen each time to control by palpation, the amount of heat being disseminated through the uterus and adjacent structures. This he considers to be an absolute *sine qua non*, if satisfactory results are to be obtained. He says that he now routinely ties both internal iliac arteries, to aid in starvation of the growth, and to prevent the danger of secondary hemorrhage which previously occurred in several cases.

DERMATOLOGY

UNDER THE CHARGE OF

MILTON B. HARTZELL, M.D.,

PROFESSOR OF DERMATOLOGY IN THE UNIVERSITY OF PENNSYLVANIA.

A Tumor-like Form of Lupus.—FISCHER (*Dermat. Ztschr.*, April, 1915) reports an unusual case of lupus, characterized by numerous tumor-like lesions, occurring in a young Russian, twenty-two years old, who was at first suspected to be suffering from leprosy. The left leg, which was notably enlarged and elephantiasic in appearance, was the seat of numerous discrete and confluent tumors varying in size from a pea to a cherry, and many cicatrices. The histological and bacteriological study of the case demonstrated its tuberculous nature. The cutaneous affection was most probably secondary to an osseous tuberculosis of the leg beginning inchildhood. Fischer insists upon the strict separation of these tumor-like cases from other forms of cutaneous tuberculosis, such as the papillomatous proliferations which occasionally occur in ulcerating lupus, tuberculosis verrucosa cutis and lupus verrucosus, with which they have nothing to do.

Congenital Familial Hereditary Alopecia the Result of Hypothyroidism.—PETERSEN (*Dermat. Ztschr.*, April, 1915) reports an example of hereditary alopecia occurring in three generations, affecting equally the male and female members of the family, and limited strictly to the scalp. The affected individuals were born with a normal growth of hair which continued to grow normally until about the fourth or sixth year. It then began to fall out and lose its pigment, becoming completely colorless, and continued to do so until at puberty or a little later the scalp was completely bald. In three children of the family under Petersen's observation the administration of thyreoidin, in doses of 3 to 9 centigrams daily, was followed by good results. After about eight months of this treatment the hair ceased to fall and regained its color. The favorable result following the administration of thyreoidin leads Petersen to conclude that the affection was due to deficient endocrine secretion the result of diminished activity of the thyroid gland.

Pemphigoid Eruptions Following Vaccination.—MOOK (*Jour. Cutan. Dis.*, October, 1915), in an interesting paper on this important subject, sums up the result of the study of his own cases and of those in literature as follows: The cases may be divided into three groups: (A) those which terminate in rapid recovery and may or may not be accompanied by constitutional disturbance; (B) those which continue as a chronic recurrent vesicular or bullous affection which may or may not be accompanied by constitutional disturbance; (C) a third group which terminates rapidly in death. The period of incubation varies from three or four days to four months, the average period being in the

majority of cases from three to five weeks. In the benign cases the bullæ are smaller than in the severe ones. The eruption shows a predilection for the neighborhood of the mouth, the neck, and extremities, particularly the joints. Inoculations in monkeys, a calf, guinea-pigs and rabbits were negative. Blood cultures from a fatal case and from two which recovered were negative under various conditions and on various media. Ordinary staphylococci were obtained from cultures made from the contents of some of the bullæ while others were found sterile.

Trichloracetic Acid and its Uses in Dermatology.—Davis (*Jour. Cutan. Dis.*, October, 1915) thinks trichloracetic acid has a selective action upon epithelial tissues and finds it most useful in the treatment of a number of cutaneous affections where a somewhat superficially acting cauterant is indicated. In patches of degenerative seborrhea and in pigmented moles its use is followed by satisfactory results. The skin is cleansed with benzine to facilitate the penetration of the acid which may be applied with a toothpick wrapped with a bit of cotton. It is particularly useful in pigmentations, papillomata and nevi. In xanthoma palpebrarum Davis regards it as the ideal remedy. In fissures in the region of the mouth and nares and about the anus he has found it invaluable.

The Relation of Animal to Human Sporotrichosis.—Meyer (*Jour. Amer. Med. Assn.*, August 14, 1915), since 1911, has been investigating the reported cases of the transmission of sporotrichosis from the horse to man, most of the work being done in Pennsylvania where sporotrichosis in horses is a common affection. The evidence which he collected does not support the theory that the malady is very frequently transmitted from the horse to man. Only two cases of human sporotrichosis have been recorded in Pennsylvania, and in one of these infection by contact with a sporotrichotic horse was at first suggested but could not be proved conclusively. The absence of the affection among veterinarians and farmers in Pennsylvania where it is very common in the horse demonstrates, in Meyer's opinion, that sporotrichotic infection in man by contact with the horse occurs only very rarely.

Lupus Erythematosus of the Mucous Membranes.—Culver (*Jour. Amer. Med. Assn.*, August 28, 1915) reporting eleven cases of lupus erythematosus affecting various mucous membranes, announces it as his belief that the mucous membrane lesions as well as those upon the skin are the result of a general disease, the evidence pointing to digestive and assimilative faults as the most important causes. He concludes that internal treatment and a proper regimen are quite as necessary as local treatment. In the discussion which followed the reading of the paper Pusey expressed his belief that lupus erythematosus is a toxic dermatosis, belonging in the erythema multiforme group.

Bullous Dermatitis Caused by the Colon Bacillus.—Potter (*Jour. Cutan. Dis.*, April, 1915) reports the case of a young woman who one month after a normal labor was seized with convulsions, the origin

of which could not be determined. During the patient's second week in the hospital an erythema appeared on the arms and face which disappeared in the course of three or four days except upon the face where it persisted. A bullous eruption then appeared upon the hands, forearms and ankles accompanied by slight elevation of temperature (101°). Nothing abnormal was found in any of the viscera, and smears taken from the cervix and vagina shows nothing. Cultures made from the contents of the blebs revealed a type of the colon bacillus. The bullous eruption spread to the face, shoulders, buttocks and lower limbs, and new lesions continued to appear throughout the course of the illness which lasted about six weeks, running an irregular course similar in some respects to typhoid fever, but the Widal reaction was repeatedly negative. The treatment consisted in the employment of an autogenous vaccine which Potter thinks was of benefit in checking the appearance of the blebs.

Paraphenylene Diamene Dermatitis.—BUNCH (*Brit. Jour. Dermat.*, September, 1915) has recently had under his care a number of cases of a severe dermatitis resembling in appearance a weeping eczema, situated upon the scalp and face resulting from the use of paraphenylene diamene used as a hair dye. In severe cases the dermatitis affects the entire face and may spread to the chest and back. While this dermatitis may follow the first application it may not appear until it has been applied a number of times. (I have seen a number of cases of a like kind in the past year in all of which the cause was entirely overlooked, no suspicion being entertained by the patient or her physician that the dye had anything to do with the dermatitis which was supposed to be an eczema.—M. B. H.)

Etiology of Erythema Nodosum.—ROSENOW (*Jour. Cutan. Dis.*, May 1915), at the clinical session of the 38th Annual Meeting of the American Dermatological Association, demonstrated cultures of a markedly pleomorphic organism obtained from the subcutaneous nodes in six typical cases of erythema nodosum, which he believes to be the cause of the disease. The same organism was also obtained from a cervical gland draining an infected tonsil in one case, from the focus of infection (tonsil and superficial ulcer on the anterior pillar) in two cases, and from the blood in pure cultures in two cases. Injected intravenously into dogs, rabbits and guinea-pigs, it exhibits a remarkable affinity for the subcutaneous tissues, producing localized subcutaneous hemorrhages followed by infiltration, migration of leukocytes, and enlargement of neighboring lymphatic glands. The hemorrhages are frequently symmetrically distributed, and from the hemorrhagic areas the organism has been isolated repeatedly. In smears from original colonies the organisms presents all gradations between bacilli, elongated diplococci and cocci, the form probably depending upon conditions of environment.

The Vaccine Treatment of Ringworm of the Scalp.—STRICKLER (*Jour. Cutan. Dis.*, March, 1915) reports seven cases of ringworm of the scalp cured by injections of a vaccine prepared by growing the infecting organism upon "French Proof Agar" in an Erlenmyer flask, triturating the cultures thus obtained with crystals of chemically pure

sodium chloride and afterward adding enough sterile distilled water to make a normal salt solution. The vaccine was preserved by the addition of 0.25 per cent. phenol. The dose varied from 1 c.c. to 2 c.c. given at intervals of three days. After the patient has had 6 or 7 injections an infiltrated area appeared in some cases at the site of the injection about thirty-six hours after it. In one case abscesses followed the injection of the vaccine and the treatment had to be discontinued. The number of injections varied from seven to seventeen. Strickler concludes from his experience with these cases that ringworm of the scalp can be cured by vaccines, but is not prepared to state in what proportion of the cases treated a cure can be obtained in this manner.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

JOHN McCRAE, M.D., M.R.C.P.,

LECTURER ON PATHOLOGY AND CLINICAL MEDICINE, MC GILL UNIVERSITY, MONTREAL; SOME TIME PROFESSOR OF PATHOLOGY IN THE UNIVERSITY OF VERMONT, BURLINGTON, VERMONT; SENIOR ASSISTANT PHYSICIAN, ROYAL VICTORIA HOSPITAL, MONTREAL,

AND

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY AND BACTERIOLOGY, UNIVERSITY OF PITTSBURGH, PITTSBURGH, PA.

Nature and Clinical Importance of Pseudodiphtheria Bacilli.—Numerous workers have called attention to the finding of organisms closely resembling B. diphtheriæ, in various parts of the body. Such organisms have now been recognized as normal inhabitants of the nose, throat, ear, genitalia and skin. Under such conditions these bacteria have no significance. But the question whether these organisms can be important factors in disease processes under abnormal conditions is far from clear. Fox (*Jour. Med. Research*, 1915, xxxii, 309) has made a study of the diphtheroids in an attempt to throw some light upon their relationship to disease. Four groups of organisms are commonly recognized: (1) true diphtheria bacilli; (2) avirulent members of group one; (3) pseudodiphtheria organisms which morphologically resemble group one and two, but differ culturally and (4) organisms belonging to the so-called Hoffman group which, although bearing a basic resemblance to the above three groups, differ both morphologically and culturally. The last group has also been spoken of as pseudodiphtheria. Not a little importance has been placed upon the various members of the pseudodiphtheria bacilli in crediting them with peculiar pathogenic qualities. Thus some importance has been placed upon their presence in otitis media, vaginitis, coryza and lesions of the lymphatic glands. In all instances where the organism is found in external ulcers it is in mixed culture. Pure cultures, however, have been isolated from the

blood, spleen, lymph glands and body cavities at autopsy. The reports of these findings are in the majority of cases not clear in indicating the pathogenic qualities in man. The author expresses a desire for more thorough tests and studies of the pseudodiphtheria organism when isolated from conditions in which they appear an important etiological factor. Immunity tests and sugar reactions are particularly called for. The author points out that the results reported in Hodgkin's disease by various authors are not uniform and evidence is not available that the organisms isolated and reported are the same. With the wide-spread dissemination of members of the pseudodiphtheria group, their presence in mixed infections has been looked upon with little importance. Fox reports the isolation of these bacteria from 20 different cases, in only one of which did it appear to have an important bearing. In the majority of instances the organisms gain entrance to the body by the respiratory and genito-urinary tracts. Existing as saphrophites upon the mucous membranes they probably continue a non-parasitic or symbiotic existence in the animal body. What relation these pseudodiphtheria bacilli may bear to the avirulent B. diphtheriæ, is not known. The author was unable to bring about mutation of the true B. diphtheriæ by methods of culture.

Tumors of the Parathyroid Glands.—There have been relatively few reports of parathyroid tumors, the majority of which have been found by accident at autopsy. In only a few instances did they cause symptoms of a character that would have a bearing upon the functions of the glands. HARBITZ (*Jour. Med. Research*, 1915, xxxii, 361) has collected the cases in the literature, the first of which was reported by De Santi in 1900. The author points out that all of the tumors reported cannot be acepted as of parathyroid origin. Not a few of them are described in intimate association with the thyroid. The author adds 2 new cases of parathyroid tumors, one of which was associated with osteomalacia and the other with paralysis agitans. In view of the work of McCallum on the increased calcium output in disturbances of parathyroids this association with osteomalacia is very significant. The presence of parathyroid disease in paralysis agitans has previously been observed by other Norwegian authors.

Splitting of the Elastic Fibers in Arteries.—In the pathological classification of arteriosclerosis not a little weight has been placed upon the minute histological findings in diseased arteries. The alterations observed in the elastic tissue of arteries have constantly attracted attention until Jores, in 1903, gave an over-important place to this finding. According to him, and his views have been widely propagated in text books, the splitting of the internal elastic lamina in arteries was a process associated with hyperplasia of the musculo-elastic layer and their presence in an artery indicated true arteriosclerosis. At that time it was pointed out that these organic changes in muscle and elastic fibers were prone to show degenerative changes of a fatty nature. Jores claimed that the splitting of internal elastic lamina was only obtained in the presence of contiguous muscular hyperplasia. In this study by MCMEANS (*Jour. Med. Research*, 1915, xxxii, 377) it is shown that such splitting may occur in the absence of muscle changes

and are found in the vicinity of inflammatory processes. Arteries obtained from inflammatory lesions of diphtheria, septicemia, typhoid fever, pneumonia, and chorea were all shown to have developed a splitting of the internal elastic fiber. A similar result was observed in the neighborhood of endothelial proliferative responses where fatty streaks of the intima were present. It is thus shown that the nature of this lesion is not specific as was claimed by Jores. Thus if the splitting of the elastic lamina is a characteristic of one of the types of arteriosclerosis the etiological factors bringing it about are multiple.

Spontaneous Rupture of the Kidneys in Acute Toxic Nephritis.—Rupture of the kidney is usually a surgical condition of traumatic origin. Spontaneous rupture on the other hand is an infrequent process resulting from a slowly progressive pathological condition within the organ itself. In all, some 30 cases have been reported. Perirenal hemorrhage is obviously a constant finding. This hemorrhage may result from renal arteriosclerosis, interstitial nephritis and acute parenchymatous nephritis or from renal neoplasms, tuberculosis, abscess and infarct. The case reported by Wade (*Jour. Med. Research*, 1915, xxii, 419) was one of a negro of twenty years with acute parenchymatous nephritis. Both kidneys were markedly swollen with multiple ruptures through the capsule. Curiously enough no symptoms indicated this serious damage during life.

Thyroid and Circulatory Changes following Experimental Ligation of the Thyroid Vessels.—Newhof (*Jour. Med. Research*, 1915, xxxii, 501) experimented upon dogs to determine the effect of ligation upon the thyroid. He points out that much care must be taken in the interpretation of the results in that the histology of the thyroid is far from uniform and that certain traumata induced during the operative procedure are apt to bring forth organic changes not dependent upon the vascular occlusion. Uniform results do not follow the ligation of the thyroid arteries or veins. More marked effect was obtained upon ligation of the veins than of the arteries. At the end of several months the alveoli are increased in size, while some increase of connective tissue may be observed. The interference with the arterial supply showed mainly a diminution in the size of the acini. In general, the results obtained by the author are so slight that this method of operative approach for the enlarged thyroid does not appear very encouraging.

The Origin of Local Eosinophilia.—The presence of a local eosinophilia in tissues is not an uncommon observation. It is most commonly seen in certain specific infections, chronic granulation tissue, and peculiar lesions such as are found in anaphylaxis. Considerable controversy has developed as to the origin of these eosinophiles. Some claim they migrate from the hemopoietic organs, others that they arise locally from mixed tissue cells of the injured part. Photakis (*Ztschr. f. Exper. Path. u. Therap.*, 1915, xvii, 270) studied the development of local eosinophilia in anaphylactic shock. Under these conditions it has been repeatedly found that the lungs have become the site of great accumulations of eosinophiles. The author found that the sensitizing dose, using serum, did not alter the numerical cellular

state, nor did bone-marrow show any change at the moment before the active anaphylactic dose was given. Having furthermore treated the animals with intravital strains, he was able to show that the local tissues in the lungs played no part in the production of the eosinophilia subsequently developing in it. He was also able to observe the direct migration of the eosinophiles into the interstitial tissues from the lung capillaries. Quite marked cellular changes indicative of an overproduction of eosinophiles occurred in the bone-marrow.

Bacteria of Plant Tumors as Causative Agents of Human Disease.—FRIEDEMANN, BENDIX, HASSEL and MAGNUS (*Ztschr. f. Hygiene*, 1915, lxxx, 114) believe that they have established an animal and vegetable pathogenicity for the B. tumefaciens. On four separate occasions they isolated a Gram-negative bacillus (actively motile, showing acid on litmus whey, acid and gas on dextrose and lactose, no fermentation of saccharose, liquefaction of milk and a luxurient shiny growth on agar) from a case of suppurative arthritis and 3 cases of suppurative meningitis. These organisms have the biological characters of B. tumefaciens, as described by Smith and Jensen. The serum reactions, however, of one of the strains differs markedly from the others, as well as from the Jensen organism. This aberrant strain they claim agreed with the reactions of another strain of B. tumefaciens. They believe that there are two types of this organism distinguishable only through the serum reaction. In 2 of their cases of meningitis they observed the presence of meningococcus in direct smears but were not able to isolate them on their cultures and the organisms subsequently isolated had not been observed in the direct smears. The organisms obtained from the human did not produce any type of tumor growth in plants. All of the cultures had more or less pathogenicity for small animals. A similar organism has been isolated from the feces of those suffering from colitis.

Phagocytic Properties of the Eosinophile and the Absorption of Toxic Products of Vermes.—The phagocytic property of eosinophiles is well established and has been studied by various authors. WEINBURG and SEQUIN (*Ann. de l'Inst. Pasteur.*, 1915, xxix, 32) have taken up the study of the importance of this phagocytosis and also the conditions under which it manifests itself. The authors studied the action of the eosinophile in the role of the phagocyte both *in vitro* and *in vivo*. *In vitro* they observed its reaction toward (1) inert substances; (2) various bacteria; (3) protozoa; (4) red blood cells. They found that the eosinophiles possess the power of engulfing inert materials and also of phagocyting the majority of bacteria as well as protozoa and red blood cells. Many of the bacteria, protozoa and red cells were completely digested by the eosinophiles. *In vivo* the authors studied phagocytosis by the eosinophiles in the peritoneal cavity, in the adjacent subcutaneous tissue, and in the circulating blood of the guinea-pig. They found that the phenomenon takes place with equal readiness in each of these situations and when the eosinophiles are very abundant in the blood or when they are massed together at the point of entrance of the bacteria they play an important part in protecting the organism

from infection. However, these eosinophiles play only a secondary role in phagocytosis as their presence is rather infrequent in purulent collections. Sufficient recognition is not accorded the eosinophile because the bacteriological staining technique does not usually permit of the differentiation of the various kinds of leukocytes. A third seires of experiments was undertaken to demonstrate the inhibition of phagocytosis by the use of the liquid from hydatid cysts. The eosinophiles, having been subjected to the hydatid liquid for an hour at 37°, no longer showed evidence of their phagocytic qualities, although the other leukocytes retained their power of engulfing organisms. The authors state that eosinophiles from immunized animals absorb the hydatid antigen more readily than do those of normal animals. They conclude that the eosinophile leukocytes play an important role in immunity and are especially adapted to neutralizing toxic substances of certain parasites.

Primary Melanosarcoma of the Adrenals.—MACLACHLAN (*Jour. Med. Research*, 1915, xxxiii, 93) gives a description of an unusual tumor of the adrenal occurring in a male of forty-eight years. The tumor was a bilateral melanosarcoma with extensive metastases. Macroscopically the tumors were roughly triangular in shape, somewhat suggestive of the normal adrenal and almost equal in size (measurements 10 x 8 x 4 cm.). The primary and secondary growths were all intensely pigmented. There was no trace of normal adrenal either in the gross or in microscopic sections. In discussing the origin of the tumor the author concludes that there was a primary site in both adrenals arising from chromatophore cells which were probably congenitally aberrant. The absence of any bronzing of the skin and mucous membranes with complete destruction of the adrenals was emphasized. The skin, in fact, appeared pale and of a leaden color. The possibility of the sympathetic ganglia taking on the adrenal function with the prevention of pigmentation in the skin as is sometimes seen in Addison's is considered as an explanation, but another hypothesis is offered. The amount of pigment formed by the primary tumor and its secondaries is excessive, and possibly accounted for all the melanin which was being produced. It would appear further that the tumor cells had greater power to produce melanin than the skin. The author takes for granted that the pigmentation of the skin seen in Addison's disease is due to substances of the melanin group.

Note to Contributors. — All communications intended for insertion in the Original Department of this JOURNAL are received only *with the distinct understanding that they are contributed exclusively to this* JOURNAL.

Contributions from abroad written in a foreign language, if on examination they are found desirable for this JOURNAL, will be translated at its expense.

A limited number of reprints in pamphlet form, if desired, will be furnished to authors, *provided the request for them be written on the manuscript.*

All communications should be addressed to—

DR. GEORGE MORRIS PIERSOL, 1913 Spruce St., Philadelphia, Pa., U. S. A.

INDEX

A

Aaron, C. D., roentgen-ray in gastro-intestinal affections, 330
Abdominal Cesarean section, 615
Aborted pneumonia and mistreatment of pneumonia, 914
Abscess, camphor, 913
  cerebellar, in a child, 147
Achylia gastrica, 72
Acro-ataxia and primo-ataxia, 651
Adler, H., value of rectal feeding, 562
Adnexal inflammation, etiology of, 919
Age mortality, statistics of, 372
Agglutination of Spirocheta pallida, 598
Allen, F. M., prolonged fasting in diabetes, 480
  treatment of diabetes, 600
Alopecia, 921
Ameba colitis, 299
Amnesia, 460
Amphibia, tumors in, 311
Anatomy of imperfectly descended testes, 762
Anders, J. M., certain syphilitic affections of heart and aorta, 835
Anderson, H. B., appendicitis as a sequela of tonsillitis, 541
Anemia, pernicious, 602
  splenectomy in treatment of, 456
Anesthesia, Kulenkampff's, 905
  in labor, 616
Aneurysms, gunshot, treatment of, 603
Anthrax spores found in earth, 778
Antibacterial action of coins on media, 778
Antithrombin in the blood, 599
Antitoxin in tetanus, 764
Appendicitis, bacteriology of, 602
  as a sequela of tonsillitis, 541
Arrhythmia, cardiac, use of digitalis in, 911
Arrhythmias, digitalis, 352
Arterial degeneration, 310
Arteries, splitting of elastic fibers in, 925
Arterio-anastomosis, futility of, in gangrene, 294
Arteriosclerosis, 827
Arthropathies, luetic, 733
Ashford, B. K., studies in moniliasis of the digestive tract in Porto Rico, 680
Auer, E. M., brain syphilis, 359
Aural sounds of muscular origin, 465
Auto-infection complicating pregnancy, 769

B

Bacilli carriers, typhoid, 613
Bacillus, Bulgarian, in cystitis and pyelitis, 461
  colon, 922
  tetanus, 779
Bacteria of plant tumors, 927
Bacterial therapy of typhoid fever, 598
Bacteriology of appendicitis, 602
  in typhoid fever, 758
Balantidiosis, 289
Barton, W. M., removal by caffein of some digitalis arrhythmias, 352
Beer, E., ligation of portal vein in suppurative portal phlebitis, 548
Biological studies on eosinophilia, 446
Birth palsy, 916
  polyneuritis in, 155
Bladder tumors, desiccation treatment of, 761
  diagnosis of, 761
  fulguration in treatment of, 761
  ulcer in women, 153
Blood, antithrombin in, 599
  in chronic lead poisoning, 902
  eclampsia and sugar in, 151
  rest N. in, as method of testing renal function, 902
  studies of, in variola and vaccinia, 138
  sugar, determination of, by polarization and reduction methods, 139
  transfusion, 36
    in children, 886
  uric acid determination in, 902
Blood-pressure determinations, 903
  and glaucoma, 305
  influence of athletic training on, 426

Boggs, R. H., value of radium in treatment of malignancy, 30
Bone, periosteal regeneration of, 293
Brachial plexus, neurolysis of, 608
Bradner, M. R., elimination of acetone and diacetic acid in surgical cases, 727
Brain syphilis, 359
Bulgarian bacillus in cystitis and pyelitis, 461
Bullous dermatitis caused by the colon bacillus, 922
Burnham, A. C., administration of glucose solutions as a prophylactic against postoperative shock, 431
Bursitis, subacromial, 115
Butyric acid sclerosis of arteries, 466

C

Cadwalader, W. B., cases resembling pseudosclerosis and progressive lenticular degeneration, 556
Calculi, ureteral, 292
Callender, G. R., gastric glands in Meckel's diverticulum, 69
Camphor abscess, 913
Cancer, gastric, 625
in mice, 307
resection of jaw for, 1
of thyroid in Graves's disease, 311
uterine, sodium treatment of, 908
Carcinoma of uterus, treatment of, by the Percy cautery, 920
Cardiac arrhythmia, use of digitalis in, 911
pictures, acute, 258
Cardiorrhaphy, late results of, 335
Cardiovascular disease, syphilis in hypertensive, 178
Carman, R. D., roentgen diagnosis of gastric cancer, 625
Carotids, common, compression of, in epilepsy, 365
Cerebral intoxications, 913
meningism and meningitis, clinical distinctions between, 913
Cesarean section, abdominal, 615
Charcoal, blood, in treatment of diarrhea, 295
Chorea complicating pregnancy, 771
relationship of, to syphilis, 766
Christian, H. A., studies of nephritis, 655
Citrate method of blood transfusion in children, 886
Clinical and pathological study of infants, 915
Colon bacillus, 922
Complement-fixation in diagnosis of pulmonary tuberculosis, 781
Congenital familial hereditary alopecia the result of hypothyroidism, 921
Cough, whooping, 763
Craig, C. F., complement-fixation in diagnosis of pulmonary tuberculosis, 781
Crotalin treatment of epilepsy, 146
Cryptogenetic peritonitis, 607
Cummer, C. L., recurrent pneumothorax, 222
Cunningham, W. F., Hodgkin's disease, 868

D

Degeneration, arterial, 310
Delirium tremens, effect of lumbar puncture in, 295
treatment of, with veronal, 140
Dementia precox, leukocytosis in, 445
Dermatitis, bullous, caused by the colon bacillus, 922
paraphenylene diamene, 923
Dermatology, trichloracetic acid in, 922
Detoxication of diphtheria and tetanus toxins, 597
Dexter, R., certain physical signs referable to the diaphragm and their importance in diagnosis, 200
Diabetes, 765
Allen treatment of, 600
pancreatic, 138
prolonged fasting in, 480
treatment and prognosis in, 485
Diaphragm, physical signs referable to, 200
Diarrhea in childhood, 915
Diastolic blood-pressure determinations, 903
Digitalis arrhythmias, 352
use of, in cardiac arrhythmia, 911
Diphtheria bacillus carriers, 309
and tetanus toxins, detoxication of, 597
Diphtheroids, distribution of, 624
in lesions of human tissue, 624
Disease, Hodgkin's, 245
Disinfection of the hands and abdominal skin, 604
of skin, 614
Diverticulum, Meckel's, 169
Dogs, secretion of kidneys in, 906
Drug treatment, 803
Ductless glands, relation of, to purin metabolism, 137
Dusts, effects of, in production of respiratory diseases, 779

E

Eastman, J. R., compression of common carotids in epilepsy, 365
Eclampsia and sugar in blood, 151
Edsall, D. L., observations on a case of family periodic paralysis, 169

Effects produced by placental extract, 617
Elliott, A. R., problems of nephritis from the clinical stand-point, 806
Elliott, J. A., splenic enlargement in early syphilis, 512
Emboli in the lung, localization of, 622
Emetin in entamebiasis, 97
Empyema of thorax, 449
Endocrine glands, action of lipoids isolated from, 446
Eosinophile, phagocytic properties of, 927
Eosinophilia, biological studies on, 446
origin of local, 926
Epilepsy, crotalin treatment of, 146
Erysipelas treated with whole blood, 768
Erythema nodosum, etiology of, 923
Ethyl and methyl alcohol, influence of, upon organ of hearing, 775
Etiology of adnexal inflammation, 919
of erythema nodosum, 923
Experiences in vaccine treatment, 910
External version in treatment of placenta previa, 769
Extirpation of pineal body, 757

F

Family periodic paralysis, 169
Femur, neck of the, bone graft peg in treatment of fractures of, 606
Fetal head, transverse position of, 152
Fever, hunger, in newborn, 770
scarlet, 766
Fevers, certain unclassified, 269
Fibroid uterus, intolerance of, in twin pregnancy, 917
of uterus, 150
Finney, J. M. T., gastro-enterostomy, 469
Fisher, E. D., Landry's paralysis, 791
Fistula, parotid, in external auditory canal, 777
Foote, E. M., partial resection of lower jaw for cancer, 1
Fracture of radius in childhood, 291
of ulna, green-stick, 291
Friedenwald, J., gastro-enterostomy, 469
Frothingham, C., Jr., studies of nephritis, 655
Fulguration in treatment of tumors of bladder, 761

G

Gall-stone disease, 906
Gangrene, treatment of, 294
Gas bacillus and infectious diarrhea in childhood, 915
Gastric cancer, 625
Gastric sediments and their interpretation, 402
Gastro-enterostomy, 469
Gastro-intestinal affections, Roentgen-rays in, 330
studies, 72
Gerhard, G. S., pleurisy, 209
Glaucoma and blood-pressure, 305
Elliott's operation in, 304
in the young, 305
Glucose solutions as a prophylactic, 431
Glycerophosphate, magnesium, in treatment of tetanus, 757
Graham Steell murmur, 496
Graves's disease, cancer of thyroid in, 311
Guinea-pigs, lead poisoning in, 518
Gunshot wounds of abdomen, 450

H

Hanes, F. M., luetin reaction in diagnosis of tertiary and latent syphilis, 703
Hay fever, pollen therapy in, 764
Head, G. D., gangrene of lung, 700
Heart cases showing vagus influence, 912
disease, treatment of, 912
rupture of, 148
Hemoptysis, pneumothorax for, 455
Herrick, J. B., certain medical aspects of recurrent malignant tumors, 25
Hexamethylenamin as a urinary antiseptic, 144
Higgins, W. H., luetic arthropathies, 733
Hip disease, 293
Hodgkin's disease, 245, 868
Hoover, C. F., significance of acro-ataxia and primo-ataxia, 651
Hopkins, A. H., sugar content of spinal fluid in meningitis and other diseases, 847
Hunger fever in newborn, 770
Hunt, J. R., paralytic and other persistent sequelæ of migraine, 313
Hydrochloric acid deficit, 289
Hypertrophy of right heart, 622

I

Icterus neonatorum, 152, 771
in the newborn, 149, 771
Ileus duplex, 451
Immunity, pneumococcus, 624
Immunization against measles, 767
Inactivation of pepsin by sodium chloride, 912
Infant feeding, soy bean and condensed milk in, 502
Infants, clinical and pathological study of, 915

Infants, syphilis in, 766
Infection, syphilitic, of the lungs, 195
Intraspinal therapy in syphilis of nervous system, 765
Inversion of uterus, 457, 917

J

Joslin, E. P., present-day treatment and prognosis in diabetes, 485

K

Kaolin in treatment of diarrhea, 295
Kessel, Leo, presence of tubercle bacilli in blood of tuberculosis patients, 377
Kidney function, 290
rupture of, in toxic nephritis, 926
stone in, recurrence of, 762
Klotz, O., chronic interstitial nephritis and arteriosclerosis, 827
Krumbhaar, E. H., classification and analysis of clinical types of splenomegaly accompanied by anemia, 227
Kulenkampff's anesthesia, 905

L

Labyrinth windows, 464
Landis, H. R. M., latent syphilitic infection of the lungs, 195
Lead poisoning, 902
in guinea-pigs, 518
Leishmaniasis, treatment of, 448
Lens, crystalline, effects of various kinds of rays upon, 305
Leprosy, knowledge concerning, 904
Leptomeningitis, syphilitic, 467
Leukemia, treatment of, 612
Leukocytosis in dementia precox, 445
therapeutic, 780
Leukopenia and aneosinophilia, 597
Lewis, P. A., latent syphilitic infection of the lung, 195
Lewisohn, R., citrate method of blood transfusion in children, 886
Libman, E., blood transfusion, 36
Ligation of thyroid vessels, 926
Localization of emboli in the lung, 622
Luetic arthropathies, 733
Luetin reaction in syphilis, 703
Lumbar puncture, effect of, in delirium tremens, 295
Lung, extirpation of, 156
gangrene of, 700
syphilitic infection of the, 195
Lupus erythematosus of the mucous membrane, 922
tumor-like form of, 921
Lymphocyte and natural and induced resistance to transplanted cancer, 904
Lyon, B. B. V., study of gastric sediments and their interpretation, 402
Lyons, R., mode of action and use of emetin in entamebiasis, 97

M

Magnesium glycerophosphate in treatment of tetanus, 757
sulphate in traumatic tetanus, 298
Malaria, malignant forms of, 901
Mastoid operations, 465
Meader, C. N., tubercle bacilli not stainable by Ziehl, 858
Means, J. H., family periodic paralysis, 169
Meara, F. S., heart cases showing vagus influence, 843
Measles, immunization, against, 767
Mechanism of pneumococcus immunity, 624
Meckel's diverticulum, gastric glands in, 69
Melanosarcoma of the adrenals, 928
Mellon, R. R., cultural and vaccine results in a case of Hodgkin's disease, 245
Meningism, 913
Meningitis, 913
sugar content of spinal fluid in, 847
tuberculous, 288
brain symptoms in, 767
Metabolism, nitrogen, in dermatoses, 603
protein, in pancreatic diabetes, 138
purin, 137
Methyl and ethyl alcohol, influence of, upon organ of hearing, 775
Microscopic test for pasteurized milk, 621
Middleton, W. S., influence of athletic training on blood-pressure, 426
Migraine, 313
Miller, J. L., value of symptomatic drug treatment, 803
Minot, G. R., respiratory signs and symptoms in trichinosis, 571
Moniliasis of the digestive tract, 680
Montgomery, C. M., statistics of age mortality based upon the number of persons alive at each age, 372
Moschcowitz, E., histopathology of calcification of spinous tendons as associated with subacromial bursitis, 115
Mouth infection, 145
Mucous membranes, lupus erythematosis of, 922
Mumps, inoculation against, 621
Myocardial efficiency, 582
Myxedema, pregnancy complicated by, 460

N

Nature and clinical importance of pseudodiphtheria bacilli, 924
Neonatorum, icterus, 771
Nephrectomy during pregnancy, 616
Nephritis, acute toxic, 926
  interstitial, and arteriosclerosis, 827
  problems of, from the clinical stand-point, 806
  studies of, 655
Nerve cells in the ovary, 154
Nervous system and abdominal affections, 293
Neurolysis of brachial plexus, 608
Newborn, hunger fever in, 770
  icterus of, 149, 771
Nipple, Paget's disease of, 907
Nitrogen metabolism in dermatoses, 603
Nitrous oxide gas in labor, 616
Nucleinic acid in blood diseases, 290

O

Oculocardiac reflex, 148
O'Hare, J. P., studies of nephritis, 655
Ophüls, W., lead poisoning in guinea-pigs, 512
Opium alkaloids, action of, on coronary artery, 296
Os calcis and patella, tuberosity of, for covering of stump, 760
Osborne, O. T., Raynaud's syndrome, 157
Ottenberg, R., blood transfusion, 36
Ovarian sarcoma in children, 463
Ovary, nerve cells in, 154

P

Paget's disease of the nipple, 907
Palsy, birth, 916
Paralysis, family periodic, 169
  Landry's, 791
Paralytic and other sequelæ of migraine, 313
Paraphenylene diamene dermatitis, 923
Parathyroid glands, tumors of, 925
Parotid fistula in external auditory canal, 777
Paroxysmal tachycardia, 447
Pasteurized milk, microscopic test for, 621
Patella and os calcis, tuberosity of, for covering of stump, 760
Patent ductus arteriosus, 147
Pathological and clinical study in infants, 915
Pellagra, 619
Pelvic varicocele, 773
Pemphigoid eruptions following vaccination, 921
Pepsin, inactivation of, by sodium chloride, 912
Peptic ulcer, 609
Periodic paralysis, family, 169
Periosteal regeneration of bone, 293
Perirenal apoplexy and sclerosis, 155
Peritonitis, cryptogenetic, 607
Pernicious anemia, 602
  splenectomy in, 909
Phagocytosis, mechanism of, 468
Phlebitis, 548
Pineal body, extirpation of, 757
Placenta, delivery of, 617
  previa, treatment of, 151, 769, 918
Placental extract, effects produced by, 617
Plague, geographic distribution of, 620
Pleurisy, 209
  tuberculous, 312
Pneumococcus immunity, 624
  mechanism of, 624
Pneumonia, 914
Pneumothorax, artificial, 611
  for hemoptysis, 455
  recurrent, 222
  treatment of pulmonary tuberculosis, 758
Poisoning, lead, 902
Pollen therapy in hay fever, 764
Polyneuritis in birds, 155
Pool, E. H., late results of cardiorrhaphy, 335
Portal vein, ligation of, in phlebitis, 548
Pregnancy, auto-infection complicating, 769
  chorea complicating, 770
  complicated by myxedema, 460
  duration of, 616
  nephrectomy during, 616
Prophylactic immunization against typhoid fever, 143
Protein metabolism, 138
  reactions in spinal fluid, 445
Proximo-ataxia and acro-ataxia, 651
Prurigo nodularis, 392
Pseudodiphtheria bacilli, nature and clinical importance of, 924
Pseudosclerosis and progressive lenticular degeneration, 556
Pulmonary tuberculosis in childhood, 299
Pulse, alternation of the, 82
Purin metabolism, relation of, to ductless glands, 137
Pylephlebitis complicating appendicitis, 605

R

Rackemann, F. M., respiratory signs and symptoms in trichinosis, 57

Radium treatment of inoperable uterine cancer, 908
value of, in treatment of malignancy, 30
Ramirez, M. A., late results of cardiorrhaphy, 335
Raynaud's disease, 157
syndrome, 157
Rectal feeding, 562
Rehfuss, M. E., gastro-intestinal studies, 72
Reimann, S. P., elimination of acetone and diacetic acid in surgical cases, 727
Relapsing fever, renal irritation in, 600
Renal irritation in relapsing fever, 600
Report of committee on treatment of structural scoliosis, 907
Rest N. in blood, 902
Retinal detachment, operative treatment of, 306
Reviews—
Abbott, Bacteriology, 745
Abbott, Hydrotherapy, 283
Bach, Radiation, 754
Bailey, Histology, 130
Bainbridge, Cancer, 747
Bass, Alveolodental Pyorrhea, 595
Berkeley, Obstetrics, 590
Best, The Deaf, 751
Bishop, Arteriosclerosis, 128
Blackham, Aids to Tropical Hygiene, 136
Blum, Renal Diagnosis, 285
Bonney, Obstetrics, 590
Boyd, Painless Childbirth, 591
Braasch, Pyelography, 278
Brothers, Medical Jurisprudence, 588
Bruce, Sciatica, 284
Brunton, Circulation, 745
Bulkley, Cancer, 277
Cammidge, Feces of Children and Adults, 283
Charezieux, Les Prejuges en Art Dentaire, 135
Chisholm, Recreations of a Physician, 593
Church, Nervous and Mental Diseases, 748
Comrie, Medical Dictionary, 587
Cornet, Scrofulosis, 135
Crile, G. W., The Emotions, 439
Curschmann, Text-book on Nervous Diseases, 746
Das, Obstetrics, 749
Dennett, Simplified Infant-feeding, 900
Ely, Bones and Joints, 281
Emslie, Coxa Vara, 595
Fairbairn, Text-book for Midwives, 752
Farr, Medicine, 437
Fischer, Edema and Nephritis, 898
Fiske, The Brain, 136
Reviews—
Fox, Hysteria, 286
Goddard, Feeble-mindedness, 133
Greene, Pharmacology, 594
Grotjahn, Soziale Pathologie, 890
Hare, Progressive Medicine, 438
Heitzmann, Urinary Analysis, 131
Hirschel, Anesthesia, 592
Horsley, Surgery of the Blood-vessels, 589
Hughes, Atem Kuren, 750
Ivy, Applied Immunology, 893
Jessner, Behandlung Kosmeticher Hautleiden, 135
Johns, Alveolodental Pyorrhea, 595
Johnston, Anatomy, 896
Jones, Ambidexterity, 286
Knox, Radiography, 894
Kraus, Pathologie, 751
Krause, Surgical Operations, 276
Lamb, Nose, Throat, Ear, 753
Landolt, Ocular Movements, 134
Lane, Operative Treatment of Intestinal Stasis, 898
Lhermitte, Système Nerveux, 596
Lorand, Die Menschliche Intelligenz und ihre Steigerung, 132
Mayo Clinics, 585
Mosby, Causes and Cures of Crime, 592
Murphy, Clinics, 127, 279, 892
Nash, Evolution and Disease, 900
Nordmann, Praktikum der Chirurgie, 129
Oliver, Lead Poisoning, 897
Ormsby, Skin Diseases, 274
Ott, Fever, 749
Park, Microörganisms, 275
Partridge, Psychology of Intemperance, 753
Peterson, Nervous and Mental Diseases, 748
Pope, Anatomy and Physiology for Nurses, 281
Pope, Medical Dictionary, 132
Prentiss, Embryology, 895
Roemer, Infantile Paralysis, 286
Roussy, Système Nerveux, 596
Seifert, Die Nebenwirkungen, 756
Sequeira, Skin Diseases, 587
Short, Physiology, 591
Skinner, Air, 754
Snow, Mechanical Vibration, 284
Stark, Pharmacy, 285
Stewart, Physiology, 130
Sutherland, Heart in Early Life, 899
Swanberg, Foramina, 756
Thomas, Applied Immunology, 893
Tracy, Painless Childbirth, 591
Tredgold, Mental Deficiency, 752
Underwood, Dental Anatomy and Physiology, 282

Reviews—
Vedder, Beriberi, 280
Wallace, Dental Diseases, 282
Wiggers, Circulation in Health and Diseases, 890
Wilson, Heart Failure, 755
Rickets, sex distribution of, 914
Ringworm of scalp, 923
Roentgen-rays in gastro-intestinal affections, 330
Ruhräh, J., soy bean and condensed milk in infant feeding, 502
Rupture of breast, 148

S

Sachs, E., intracranial telangiectasis, 565
Sailer, J., relative pulmonary insufficiency (Graham Steell murmur), 496
Salvarsanized serum, 763
Salvarsannatrium, 287, 909
Sarcoma, ovarian, in children, 463
Scalp, ringworm of, 923
Scarlet fever, treatment of, 766
Schick reaction, 618
Schoonmaker, H., test of myocardial efficiency, 582
Sclerosis of arteries, 466
and peritoneal apoplexy, 155
Scoliosis, structural, 907
treatment of, 109
Scopolamin-morphin amnesia, 460
Secretion of kidneys in dogs, 906
Serum, mercurialized, in cerebrospinal syphilis, 453
salvarsanized, 763
Sex distribution of rickets, 914
Sicard, M. H., heart cases showing vagus influence, 843
Silver foil, use of, in surgery, 450
Sisson, W. R., Friedländer bacillus pneumonia, 713
Skin disinfection, 604
Skull, covering of defects in, 452
Solar eclipse, impaired vision following naked-eye observation of, 306
Spinal fluid, protein reactions in, 445
Spine, typhoid, 140
Spirocheta pallida, agglutination of, 598
Splenectomy in pernicious anemia, 456, 909
Splenomegaly accompanied by anemia, 227
Splitting of elastic fibers in arteries, 925
Spontaneous rupture of kidneys, 926
Sporotrichosis, relation of animal to human, 922
Sprue, occurrence of, in United States, 692
Starvation method *versus* carbohydrate reduction in diabetes, 765
Stein, R., certain unclassified fevers, 269
Sterilization of the skin, 605
Stoll, H. F., role of syphilis in hypertensive cardiovascular disease, 178
Stone in kidney, recurrence of, 762
Sugar content of spinal fluid in meningitis, 847
Symptomatic drug treatment, 803
Syphilis, brain, 359
congenital, 300
early, splenic enlargement in, 512
in hypertensive cardiovascular disease, 178
in infants, 766
luetin reaction in, 703
mercurialized serum in, 298
relationship of, to chorea, 766
treatment of, with salvarsanized serum, 455
Syphilitic affections of heart and aorta, 835
infection of the lungs, 195
leptomeningitis, 467

T

Tachycardia, paroxysmal, 447
Telangiectasis, intracranial, 565
Testes, imperfectly descended, anatomy of, 762
Tetanus, antitoxin in, 764
bacillus, 779
germs, destruction of, with ultraviolet rays, 296
treatment of, 146, 454
Therapeutic leukocytosis, 780
Therapy, intraspinal, in syphilis of nervous system, 765
Thompson, C. B., Friedländer bacillus pneumonia, 713
Thorax, empyema of, 449
Thorium, 461
Thyroid and circulatory changes following experimental ligation of thyroid vessels, 926
Tongue-depressor gastro-enterostomy clamp, 606
Tonsillitis, appendicitis as a sequela of, 541
Treatment of placenta previa, 918
of scoliosis, 109
Trichinosis, 571
Trichloracetic acid and its uses in dermatology, 922
Tubercle bacilli in blood of tuberculous patients, 377
not stainable by Ziehl, 858
bacillus, granular form of, 137
Tuberculosis, complement-fixation in, diagnosis of, 781
of hip, 142
of knee-joint in childhood, 141
pneumothorax, treatment of, 758

Tuberculosis, pulmonary, in childhood, 299
Tuberculous meningitis, 288
brain symptoms in, 767
pleurisy, 312
Tumor-like form of lupus, 921
Tumors in amphibia, 311
bladder, desiccation treatment of, 761
diagnosis of, 761
fulguration in treatment of, 761
malignant, 25
multiplicity of, 468
of parathyroid glands, 925
Typhoid bacilli carriers, 613
fever, 287
bacterial therapy of, 598
bacteriology in, 758
prophylactic immunization against, 143
treatment of, 295, 296
in the vaccinated, 759
vaccine therapy of, 601, 901
treatment of, 139
immunization, 613
spine, 140
vaccine, modification of, 448
treatment of, 145
Typhus fever, prevention of, 308

U

Ulcer, bladder, in women, 153
peptic, 609
of the vulva, treatment of, by salvarsan, 304
Ultraviolet ray, germicidal action of, 621
Ureter, repair of, with intestine, 774
Ureteral calculi, 292
Uric acid determination in blood, 902
excretion, 600
Urinary incontinence in the female, 462
Uterine cancer, radium treatment of, 908
fibroids complicating pregnancy, 458
Uterus, backward displacement of, 264
carcinoma of, treatment of, by the Percy cautery, 920
Uterus, fibroid of, 150, 917
inversion of, 457
with prolapse and recovery, 917
rupture of, 459
traumatic displacement of, 302

V

Vaccine therapy of typhoid fever, 601, 901
treatment, 910
of ringworm of the scalp, 923
of typhoid fever, 139, 145
typhoid, modification of, 448
and variola, studies of blood in, 138
Variability of pathogenic bacteria, 623
Varicocele, pelvic, 773
Variola and vaccinia, studies of blood in, 138
Vision, impaired, 306
Vulva, ulcer of, treatment of, by salvarsan, 304
Vulvovaginitis in children, 772

W

White, P. D., alternation of the pulse, 82
Whooping cough, 763
Wile, U. J., splenic enlargement in early syphilis, 512
Williams, C. M., prurigo nodularis and lichenification with tumor formation, 392
Williams, P. F., causes of backward displacement of the uterus, 264
Willson, R. N., diagnosis between primary and secondary acute cardiac pictures, 258
Wood, E. J., occurrence of sprue in United States, 692
Woods, Alan C., studies of nephritis, 655

Y

Young, J. K., treatment of scoliosis, 109

MAR - 1 1945

Corpus Luteum.
True substance. Powder; 2 grain and 5 grain capsules; 2 grain tablets.

Pituitary Liquid.
Physiologically standardized. Free from preservatives. 1 c.c. ampoules.

Pituitary Powder
and 1 grain tablets (whole gland).

Pituitary Powder
and 2 grain tablets (anterior lobe).

Pituitary Powder
and 1/10 grain tablets (posterior lobe)

Duodenin.
1 grain tablets.

Elixir of Enzymes.
Adjuvant and vehicle.

Red Bone Marrow.
Hematogenetic. Histogenetic.

Lecithol.
Emulsion of Lecithin from brain substance.

Chymogen.
In infant feeding prevents formation of curds in milk.

Peptonizing Tablets and Peptonizing Powder.
For predigesting foods.

Thyroids U. S. P.
Powder, standardized.

Thyroid Tablets.
Standardized. 2 gr. 1 gr. ½ gr. ¼ gr.

Pineal Substance—
Powder.

Pineal Tablets—
1/20 grain.

Nutrient Wine of Beef Peptone.
Predigested beef in palatable form.

Pepsin, U. S. P.

Pancreatin, U. S. P.

Rennet, 1:30000

And a full line of organotherapeutics.

Armour's
LABORATORY
PRODUCTS

THE Armour laboratory products are made from fresh raw material taken from Federal inspected stock. The laboratory is located near the abattoirs, which enables us to put the glands and membranes into process before any deterioration has set in. All desiccating is done in vacuum dryers at a temperature that prevents injury to active principles, etc. The physician that specifies Armour's gets the best.

Literature to medical men on request.

ARMOUR & COMPANY
CHICAGO

IN PRESS

An

Autobiography

BY

EDWARD L. TRUDEAU, M.D.

LEA & FEBIGER, PHILADELPHIA

Diphtheria Antitoxin of the highest type.

We have been manufacturing it for twenty years

When (in 1894) we undertook the manufacture of diphtheria antitoxin, we had one dominant ambition: to produce an antitoxin that should leave nothing to be desired—an antitoxin that the physician might administer at a critical moment with assurance that it would not fail him. In all the years that have since elapsed we have never once lost sight of that ideal.

Diphtheria antitoxin that is carefully, scientifically, conscientiously made demands a large expenditure of time and money. The cost is amply justified. The value of a human life cannot be measured in dollars and cents. We produce the best possible antitoxin, and we spare no expense in doing it.

Unreliable antitoxin—antitoxin prepared under the handicap of inexperience or inadequate facilities—is dangerous. It gives a false sense of security. It is an injustice to the physician, a menace to his patient.

CONCENTRATED

Antidiphtheric Serum

(GLOBULIN)

is obtained from the blood of healthy, vigorous horses. It is perfected in laboratories that afford unequalled facilities for serum manufacture. It is exactingly standardized, and is carefully tested bacteriologically and physiologically. It is guaranteed as to purity and potency.

SYRINGE CONTAINERS.

Bio. 15— 500 antitoxic units.	Bio. 19— 4000 antitoxic units.
Bio. 16—1000 antitoxic units.	Bio. 20— 5000 antitoxic units.
Bio. 17—2000 antitoxic units.	Bio. 21— 7500 antitoxic units.
Bio. 18—3000 antitoxic units.	Bio. 22—10,000 antitoxic units.

SPECIFY "P. D. & CO." ON ORDERS TO YOUR DRUGGIST.

Home Offices and Laboratories,
Detroit, Michigan.

Parke, Davis & Co.

The IDEAL ELECTRICAL ILLUMINATING OUTFIT

For every purpose and use. The most practical and convenient outfit for Physicians and Surgeons where a good light is required, and an advantage in making his emergency calls, in examining and treating the Throat, the Nares, the Ear and for many other uses. This complete outfit with all attachments including Tongue Depresser, Ear Speculum, and curved and straight metal attachments for the Mouth, Etc., and regular pen light which carries in the pocket like a fountain pen, and also including three separate light attachments, mailed anywhere on receipt of **$3.50.** *Literature on request.*

IDEAL ELECTRICAL SUPPLY COMPANY

299 Broadway - - - NEW YORK CITY

BOYLSTON MEDICAL PRIZE QUESTIONS

December 31, 1915—*A prize of $300 and a Boylston Medal will be awarded for the best dissertation on the results of original research in Medicine, done by the writer.*

FOR PARTICULARS APPLY TO **H. C. ERNST, M.D., Sec'y** Address, Harvard Medical School BOSTON, MASS.

SARATOGA SPRINGS MEDICAL SANITARIUM

For gastro-intestinal, nutritional and allied disorders. Modern diagnostic therapeutic equipment. Physicians referring patients will receive laboratory and case reports of same. Open all the year. Reservations in advance.

H. E. BARIGHT, Medical Director. Saratoga Springs, N. Y.

NEW WORK **JUST READY**

CANCER

ITS STUDY AND PREVENTION

By HOWARD CANNING TAYLOR, M.D.

Gynecologist to the Roosevelt Hospital, New York; Professor of Clinical Gynecology, Columbia University; Member of the American Society for the Control of Cancer.

12mo, 330 pages. Cloth, $2.50, net

The author's purpose in this work is to put in readily available form every essential point of information in regard to cancer, its causes, prevention and surgical treatment. Much of the material presented is based on the author's study and observation in his extensive hospital experience. This is supplemented by data derived from official reports, and from the literature, which has been carefully weighed and scrutinized. Prof. Taylor views the cancer problem in its broader aspects, and presents information not only for the physician's use, but for him to disseminate among the laity in an effort to reduce the cancer death rate. He lays emphasis on the causes of cancer with a view to its possible avoidance; on the earlier symptoms by which it may be recognized, and on the possibility that favorable results may be obtained at slight risk by early surgical intervention.

706-8-10 Sansom St. PHILADELPHIA **LEA & FEBIGER** PUBLISHERS 2 W. 45th Street NEW YORK

NEW WORK **JUST READY**

THE DISEASES OF THE

NERVOUS SYSTEM

A Text Book of Neurology and Psychiatry

By SMITH ELY JELLIFFE, M.D., Ph.D.

Adjunct Professor of Diseases of the Mind and Nervous System in the Post-Graduate Medical School and Hospital; Visiting Neurologist to the City Hospital; Consulting Neurologist to the Manhattan State Hospital, New York, N. Y.

AND

WILLIAM A. WHITE, M.D.

Superintendent Government Hospital for the Insane; Professor of Nervous and Mental Diseases Georgetown University and George Washington University; Lecturer on Mental Diseases, U. S. Army and U. S. Navy Medical School, Washington, D. C.

Octavo, 797 pages, with 331 engravings and 11 plates. Cloth, $6.00, net.

This work represents a distinct advance in method and plan as regards the presentation of the established facts of Neurology and Psychiatry for students' use or for reference. In succinct form but with didactic clearness and in enlightening detail, two of the most eminent of American neurologists present the proven and useful from the vast accumulations of modern knowledge of nervous and mental disorders.

The author's plan provides an orderly perspective of the functions and disorders of the nervous system. The diseases are considered in order conforming to the evolutionary development of the nervous system, beginning with those bio-physical and bio-chemical symptoms which are indicative of disturbance of the vegetative nervous system—the lowest level. Next in order are taken up disorders more closely confined within the sensori-motor systems, and in conclusion are discussed the diseases which involve the psychical processes. Thus the reader passes in orderly progression from the purely bio-physical levels of unconscious automatic adjustments to the highest psychical level of conscious social adjustments.

The authors take cognizance of the latest conception of the relationship between the vegetative and psychical nervous systems, and secure unity of treatment by expressing reactions either in physico-chemical or psychological terms. They thus afford a connected treatment of the subject as a whole in place of the usual separate treatises on Neurology and Psychiatry. Avoiding philosophical theories they make the facts as observed in their most extensive personal experience their criterion in the selection of material for presentation. This work is undoubtedly destined to take front rank as a text-book or practical guide in one of the most difficult departments of modern medicine.

706-8-10 Sansom St. PHILADELPHIA

LEA & FEBIGER

PUBLISHERS

2 W. 45th Street NEW YORK

G
H

Safet
sudden c
Colds, P

Famo
qualities.

Every
teed not

Glast
Underw
of fine w

See sp

Natural Gr
Natural Gr
Natural Gr
Natural Gr
Natural Gr
Natural Gr

Glasto

GLASTENBURY
HEALTH UNDERWEAR
FOR MEN

Safety First, Last and All the Time—against sudden chilling of the body; a predisposing factor in Colds, Pneumonia and Rheumatism.

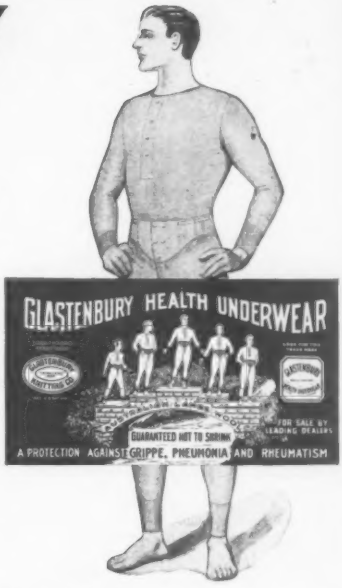
Famous over half a century for its superior qualities.

Every garment shaped to the figure and **guaranteed not to shrink.**

Glastenbury Two-Piece, Flat Knit Spring-Needle Underwear is made in fifteen grades, several weights of fine wools, worsted and merino.

See special feature of **adjustable drawer bands** on

Natural Gray Wool, **winter weight**	per garment	$1.50
Natural Gray Wool, **winter weight** (double thread)	per garment	1.75
Natural Gray Worsted, **light weight**	per garment	1.50
Natural Gray Australian Lamb's Wool, **light weight**	per garment	1.75
Natural Gray Worsted, **medium weight**	per garment	2.00
Natural Gray Australian Lamb's Wool, **winter weight**	per garment	2.50



For Sale by Leading Dealers

Write for booklet—sample cuttings. Yours for the asking.

Dept. 45

Glastonbury Knitting Company, Glastonbury, Connecticut

NEW (6th) EDITION **JUST READY** **THOROUGHLY REVISED**

A TEXT BOOK OF

PHARMACOLOGY AND THERAPEUTICS

OR, THE ACTION OF DRUGS IN HEALTH AND DISEASE.

By ARTHUR R. CUSHNY, M.A., M.D., LL.D., F.R.S.,

Professor of Pharmacology in the University of London; Examiner in the Universities of London, Manchester, Oxford, Cambridge, Glasgow and Leeds; formerly Professor of Materia Medica and Therapeutics in the University of Michigan.

Octavo, 708 pages, with 70 engravings. Cloth, $3.75, net.

Professor Cushny has brought to bear on the revision for the new sixth edition a keen appreciation of the needs and difficulties of practitioner and student. While his consideration of new drugs of demonstrated value is minutely complete, he substantially lightens the burden on the physician by eliminating from consideration many drugs and preparations of doubtful value. He has also made the essential information more readily available by a more logical arrangement, which accentuates the therapeutic aspects of the subject. His new classification is based on the organs on which the individual drugs exert their most characteristic action instead of on a consideration of all their effects as heretofore. The detailed treatment of drugs and preparations omits no point of therapeutic importance. The author's conclusions are based on careful laboratory investigations, but due regard is had to the findings of competent clinicians.

706-8-10 Sansom Street
PHILADELPHIA

LEA & FEBIGER
PUBLISHERS

2 W. 45th Street
NEW YORK

Special INFANT FEEDING

Malnutrition-Marasmus-Atrophy

MELLIN'S FOOD
4 level tablespoonfuls
SKIMMED MILK
8 fluidounces
WATER
8 fluidounces

Analysis:

Fat	.49
Protein	2.28
Carbohydrates	6.59
Salts	.58
Water	90.06
	100.00

The principal carbohydrate in Mellin's Food is maltose, which seems to be particularly well adapted in the feeding of poorly nourished infants. Marked benefit may be expected by beginning with the above formula and gradually increasing the Mellin's Food until a gain in weight is observed. Relatively large amounts of Mellin's Food may be given, as maltose is immediately available nutrition. The limit of assimilation for maltose is much higher than other sugars, and the reason for increasing this energy-giving carbohydrate is the minimum amount of fat in the diet made necessary from the well-known inability of marasmic infants to digest enough fat to satisfy their nutritive needs.

MELLIN'S FOOD COMPANY, BOSTON, MASS.

The GLEN SPRINGS

Watkins Glen on Seneca Lake, N.Y.
Wm. E. Leffingwell, Pres.

OPEN ALL THE YEAR

A Mineral Springs "Cure" and Hotel, known as THE AMERICAN NAUHEIM, from having first introduced into this country the Schott treatment for heart disease. The treatment methods and equipment embrace the best that advanced medical science has approved. Treatments are given under the direction of physicians.

THE BATHS

The Bathing Springs are similar to the waters of Bad Nauheim, but about five times as strong. **THE RADIUM EMANATION FROM BRINE SPRING NO. 2 AVERAGES 64.8 MACHE UNITS PER LITER OF WATER,** or nearly three times as much as any other American Spring known. For the treatment of **Rheumatism, Gout, Diabetes, Obesity, Neuritis, Neuralgia, Anaemia, Diseases of the Digestive System and Liver, Heart and Circulatory System, Kidney Disease, and Disorders of the Nervous System,** we offer advantages unsurpassed in this country or Europe.

The Glen Springs is situated in a large private park with miles of well-built and graded walks for Oertel hill climbing exercise. Automobiling, Boating, Fishing, Music, Dancing. Well-kept Golf Course, Tennis Courts, Miniature and Clock Golf.

Our Illustrated Booklets and Latest Reports on our Mineral Springs will be Mailed on Request

Correspondence with physicians solicited.